

BENEFIT-SHARING CASE STUDY

**The access and benefit-sharing policies of
the United States National Cancer Institute:
a comparative account of the discovery and development of
the drugs Calanolide and Topotecan.**

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INTRODUCTION

This paper examines the manner in which the United States National Cancer Institute (NCI) obtains access to genetic resources and how it shares the resulting benefits. It illustrates the evolution of the NCI's policies on access and benefit-sharing by comparing two case studies. The first case study concerns the drug candidate 'Calanolide', derived from a compound obtained from a tree species from Sarawak, Malaysia, and the second addresses another natural product pharmaceutical, 'Topotecan', derived from research on a compound originally obtained from a plant native to China.

Since the 1980s, the NCI's approach to access and benefit-sharing has evolved in response to the changing demands and capacities of governments and organisations in the countries that have provided the NCI with samples for screening ('source countries'). The NCI's approach to access and benefit-sharing has also been shaped by changes in the statutory authority of the NCI as a Federal agency of the United States government.

By comparing two very different case studies of pharmaceutical discovery and development spanning 40 years, the paper demonstrates the complex nature of drug development, with its many actors and collaborative research mechanisms. The case studies reveal how the policy framework can both facilitate benefit-sharing and constrain it, and how institutions are capable of adapting to the existing policy framework in order to devise approaches to promote benefit-sharing.

Both case studies in this paper follow the structure requested by the CBD Secretariat in its call for case studies.¹ In addition, there is a section summarising the NCI's policy on access and benefit-sharing, which is explored in greater detail in the Annexe.

OVERVIEW OF THE CASE STUDIES

THE CASE OF CALANOLIDE

ACTORS

Main actors

- **THE NATIONAL CANCER INSTITUTE (NCI)**
The NCI, one of the National Institutes of Health of the U.S. government, funded the collection of samples of *Calophyllum lanigerum* and *Calophyllum teysmannii* from Sarawak, Malaysia, and isolated the anti-HIV compounds (+)-Calanolide A and (-)-Calanolide B from them. The NCI worked on these Calanolides with Medicchem Research Inc. before granting that company rights to all further development under a license in 1995. Meanwhile, in 1994, the NCI signed a 'Letter of Collection' with the Sarawak State Government.
- **MEDICHEM RESEARCH**
This pharmaceutical company, based in Illinois, U.S.A., initially developed Calanolide compounds in collaboration with the NCI under a NIH Small Business Innovative Research

¹ <http://www.biodiv.org/bs/callbf1.html>.

Grant, then took over all further development under a licensing agreement with the NCI in 1995. The company entered into a joint venture with the Sarawak Government in 1996, under which it provides technical expertise, research facilities and training opportunities for Sarawak scientists.

- **STATE GOVERNMENT OF SARAWAK**

The State Government of Sarawak authorised NCI-funded collections of *Calophyllum lanigerum* and *Calophyllum teysmannii*. It signed a Letter of Collection agreement with the NCI in 1994. In 1996, it entered into a joint venture arrangement with Medichem Research Inc. under which it provides funding for the further development of the Calanolides.

- **SARAWAK-MEDICHEM PHARMACEUTICALS**

This joint venture between the Sarawak Government and Medichem Research seeks to complete the development and commercialisation of (+)-Calanolide A and (-)-Calanolide B. Its partners currently have a 50:50 stake in all intellectual property rights arising out of the venture.

Other actors

- **STATE FORESTRY DEPARTMENT, SARAWAK**

The Department authorised and conducted collections of *Calophyllum lanigerum* and *Calophyllum teysmannii*, in collaboration with the University of Illinois at Chicago (UIC). It has gone on to assess potential for the sustainable harvest of *Calophyllum teysmannii* as a source of (-)-Calanolide B.

- **UNIVERSITY OF ILLINOIS AT CHICAGO (UIC)**

As the NCI's Collection Contractor, the UIC conducted collections of *Calophyllum lanigerum* and *Calophyllum teysmannii* in collaboration with the Sarawak Forestry Department. It went on to assist the Department in work concerning the sustainable harvest of *Calophyllum teysmannii*.

THE GENETIC RESOURCES CONCERNED

The compound (+)-Calanolide A is isolated from the leaves and twigs of *Calophyllum lanigerum*. var. *austrororaceum*.² A sister compound, (-)-Calanolide B, is isolated in high yield from the latex of another *Calophyllum* species, namely *Calophyllum teysmannii* var. *innophylloide*.³ Both species occur naturally in the rainforests of Sarawak, Malaysia.

TYPE OF BENEFIT-SHARING ARRANGEMENT AND EXPECTED RESULTS

The benefit-sharing arrangements in this case have been established through three separate agreements: a "Letter of Collection" between the State Government of Sarawak and the NCI; a Co-operative Research and Development Agreement (CRADA) between the NCI and Medichem Research; and an agreement between Medichem Research and the State Government of Sarawak, establishing Medichem Sarawak Pharmaceuticals (SMP), a joint venture company. The monetary and non-monetary benefits include royalties, technology transfer, training and participation in scientific and biotechnological research.

² Cashman et al.: *J. Medchem*, 1992, vol. 35, 2735-2743.

³ Cragg et al.: *Ethnobotany and Drug Discovery: the Experience of the US National Cancer Institute*. Date not known.

TIME FRAME ADDRESSED

The Sarawak Forestry Department and the UIC first collected *Calophyllum lanigerum* in 1987. Within a period of just over ten years, various active Calanolide compounds were isolated, patents filed on them and research and development conducted. One product is expected to enter Phase II clinical trials this year, and another has reached the pre-clinical stage.

THE CASE OF TOPOTECAN (10-hydroxy-9-dimethylaminomethyl)

ACTORS

Main actors

- **NATIONAL CANCER INSTITUTE (NCI)**
NCI discovered the antitumour properties of *Camptotheca acuminata* in the late 1950s. The Institute funded the isolation of the tree's active compound, Camptothecin, revealed its ability to inhibit DNA and RNA synthesis, and investigated its potential as an anticancer drug until 1972. In the 1980s, the NCI co-ordinated a National Co-operative Drug Development Group (NCDDG) that resulted in further work on Camptothecin and its derivatives. The NCI undertook clinical trials of Topotecan in the early 1990s in collaboration with Smith-Kline Beecham.
- **SMITH-KLINE BEECHAM (SB)**
SB is a pharmaceutical company based in the United Kingdom, with a subsidiary headquartered in Philadelphia, Pennsylvania, U.S.A. It discovered Camptothecin's ability to inhibit Topoisomerase I, an enzyme essential to cell replication and so of great interest to cancer research, whilst collaborating with academic partners under the NCDDG. The company went on to develop and patent the Camptothecin derivative Topotecan. This compound is now marketed by SB as Hycamtin-R®.

Other actors

- **JOHNS HOPKINS UNIVERSITY (JHU); THE UNIVERSITY OF FLORIDA; THE UNIVERSITY OF VIRGINIA**
In collaboration with SB under the NCDDG, these Universities were responsible for characterising novel inhibitors of Topoisomerases, enzymes essential to cell replication and so of great interest to cancer research.
- **UNITED STATES DEPARTMENT OF AGRICULTURE (USDA)**
The USDA's Plant Introduction Programme received and grew *C. acuminata* in the early part of the century. Dr Munroe Wall, a USDA natural products researcher, supplied the NCI with samples for anticancer screening in the late 1950's. In the early 1990's, under another agreement with the NCI, the USDA investigated the commercial cultivation of *C. acuminata* in the U.S.A. as a reliable source of Camptothecin.
- **THE RESEARCH TRIANGLE INSTITUTE (RTI)**
The RTI is a non-profit, contract research organisation and is based in Durham, North Carolina, U.S.A. It was founded in 1958 by the University of North Carolina, Duke University and North Carolina State University, and a natural products laboratory was

established there in 1960. Under a contract with the NCI using NCI funding, this laboratory fractionated extracts of *C. acuminata*, leading to the isolation of Camptothecin from *C. acuminata* in 1966.

- **SUPPLIERS OF TOPOTECAN'S PRECURSOR COMPOUND, CAMPTOTHECIN**
Chinese and Indian pharmaceutical organisations supplied SB with natural Camptothecin for the manufacture of Topotecan between the mid-1980s and the early 1990s. An international broker, sourcing from Brazilian plantations, is now supplying the company.

THE GENETIC RESOURCES CONCERNED

Camptothecin is the precursor compound for the semi-synthetic drug Topotecan. It is obtained from *Camptotheca acuminata* Decaisne (Nyssaceae)⁴ and *Nothapodytes foetida* Blume (Icacinales)⁵ "Stinking Tree".⁶

C. acuminata is a rapidly-growing, deciduous tree (up to 25m) that occurs at elevations from 150m to 2,400m in South-eastern China, and may also grow in Burma and northern Thailand.⁷ Its average Camptothecin content is approximately 0.001%.⁸ The tree forms part of the Chinese mixed mesophytic forest in warm, moist, temperate regions. The northern limits to this habitat lie along the Tsinling mountains, which divide the watersheds of the Yellow and Yangtse Rivers. *C. acuminata* has been introduced to the U.S.A. on five occasions since 1911. Some seeds were sent to the USDA plant introduction garden in Chico, California, which supplied researchers working on Camptothecin in the 1960s and early 1970s.⁹

N. foetida is a small tree native to warm, broad-leaved forests in India. It has been recorded at an altitude of 1,830 meters in the Himalayan foothills, northern India, at locations including Lopchu and Rungbi, near Darjeeling, though not further east.¹⁰ It is a far richer source of Camptothecin than *C. acuminata*, with an average Camptothecin content of approximately 0.1%.¹¹

TYPE OF BENEFIT-SHARING ARRANGEMENT AND EXPECTED RESULTS

Initial sourcing of *Camptotheca acuminata* and *Nothapodytes foetida* for Camptothecin pre-dated recent international developments on access and benefit-sharing and so no formal agreements existed between the USDA or the NCI and the governments of China and India, where *C. acuminata* and *N. foetida* respectively originate. The USDA's stock of *Camptotheca acuminata* at the Chico Plant Introduction Station, California, from which it subsequently supplied samples to the NCI for anti-tumour screening in 1957, was based on a 1934 private collection by A.N. Steward of the College of Agriculture and Forestry, Nanking University, China. The sourcing of four further specimens of *Camptotheca acuminata* from a Taiwanese botanic garden in 1967, aimed at boosting supplies for research, similarly did not involve a

⁴ "Camptothecin acuminata Decaisne (Nyssaceae), Source of Camptothecin an Antileukemic Alkaloid", in Technical Bulletin No 1415, USDA, NCI and the Research Triangle Institute. Date not known.

⁵ Grierson A. J. C. & Long D. G. *Flora of Bhutan*, Volume 2, part 1. Royal Botanic Gardens, Edinburgh, 1991.

⁶ Personal communication, Dr Randall Johnson, Smith-Kline Beecham, 17 April 1998.

⁷ "Camptothecin acuminata Decaisne (Nyssaceae), Source of Camptothecin an Antileukemic Alkaloid", in Technical Bulletin No 1415, USDA, NCI and the Research Triangle Institute. Date not known.

⁸ Personal communication, Dr A. Venkatesvarlu, Dr Reddy's Research Foundation, Hyderabad, India, March 1998.

⁹ "Camptothecin acuminata Decaisne (Nyssaceae), Source of Camptothecin an Antileukemic Alkaloid", in Technical Bulletin No. 1415, USDA, NCI and the Research Triangle Institute. Date not known.

¹⁰ Grierson A. J. C. & Long D. G. *Flora of Bhutan*, Volume 2, part 1. Royal Botanic Gardens, Edinburgh, 1991.

¹¹ Personal communication, Dr A. Venkatesvarlu, Dr Reddy's Research Foundation, Hyderabad, India, March 1998.

formal agreement with the government of Taiwan. Indian researchers discovered the Camptothecin content of *Nothapodytes foetida* in 1970, quite independently of the USDA or the NCI.¹²

Supply of *C. acuminata* and *N. foetida* to the NCI and SB by pharmaceutical organisations in China and India only began in the late 1980s, when drug development studies required larger quantities of Camptothecin. Currently, SB obtains Camptothecin from a private broker that obtains plant materials from around the world. Its supplies of Camptothecin come from plantations in Brazil.¹³

Camptothecin's discovery by the RTI in 1966 was facilitated by a research contract with the NCI which funded the RTI's work. Subsequent work on a soluble form of Camptothecin, until it was dropped from clinical trials in 1972, was conducted independently by the NCI.¹⁴

The main benefit-sharing mechanism for work on *C. acuminata* in the 1980s and early 1990s was a National Co-operative Drug Development Group (NCDDG)¹⁵ involving the NCI, SB, Johns Hopkins University, and the Universities of Virginia and Florida.¹⁶ Additional co-operative mechanisms included an exchange programme co-ordinated by the NCI's Liaison Office and protocols established by the NCI's Cancer Therapy Evaluation Programme (CTEP).¹⁷ Among the benefits shared were the pooling of technology and expertise, and the relatively rapid development and approval of Topotecan as an anticancer agent. The only benefits received by the source countries that originally provided access to *C. acuminata* and *N. foetida* were revenues received in return for supplying *C. acuminata* and *N. foetida* during the discovery and development phase.

TIME FRAME ADDRESSED

Seed of *Camptotheca acuminata* was originally collected in 1911 by E.H. Wilson from Mount Omei in Szechwan Province, China, and supplied to the Arbold Arboretum. The USDA's plant introduction programme later received material collected in 1927 and 1934. After research in the 1950s and 1960s led to the identification of the active compound Camptothecin, with anti-tumour properties, the NCI undertook development work but dropped the compound from clinical trials in 1972 due to its toxicity. Only in the 1980s did work on the compound recommence, leading to the development by SB of a less toxic derivative, Topotecan, in 1986.¹⁸ Topotecan was approved by the FDA in 1996 as Hycamtin-R® and is currently on the market.

¹² Personal communication, Dr A. Venkatesvarlu, Dr Reddy's Research Foundation, Hyderabad, India, March 1998.

¹³ Personal communication, Dr Randall Johnson, Smith-Kline Beecham, 19 March 1998.

¹⁴ Personal communication, Dr Munroe Wall, Research Triangle Institute, 8 April 1998.

¹⁵ See the Annexe for further discussion of NCDDGs.

¹⁶ Personal communication, Dr Randall Johnson, Smith-Kline Beecham, 17 April 1998.

¹⁷ See the Annexe for further discussion of the CTEP.

¹⁸ Personal communication, Dr Randall Johnson, Smith-Kline Beecham, 17 April 1998.

RELEVANCE OF THE CASE STUDIES TO THE CONVENTION

CBD Article	Content	Calanolide: relevance to case study	Topotecan: relevance to case study
10	Sustainable use of components of biodiversity.	Sustainable harvest of <i>Calophyllum teysmannii</i> .	<i>Camptotheca acuminata</i> : plantations in Brazil; USDA investigation of cultivation in the USA; Chinese investigations of coppicing. <i>Nothapodytes foetida</i> : Indian ban on export of plant; forestry authorities implemented permitting system for harvesting.
15(1)& (2)	The right of sovereign states to determine national access legislation; facilitated access to genetic resources.	Federal and Sarawak access laws in Malaysia.	No access law seems to have been involved.
15(3)	Articles 15, 16 and 19 only apply to genetic resources acquired “in accordance with this Convention”: i.e. not to those obtained prior to its entry into force or from non-parties.	Not relevant. All genetic resources acquired from collections in the field under collecting permits.	USDA and other actors obtained samples of <i>C. acuminata</i> from collections made early in the twentieth century.
15(4)& (5)	Access to genetic resources on mutually agreed terms; prior informed consent for access to genetic resources.	Federal and Sarawak State Government consent (permits) for collection and research by the University of Illinois at Chicago; Letter of Collection Agreement, 1994, between Sarawak State Government and the NCI.	No access law seems to have been involved.
15(6)	Joint research.	Joint research between Sarawak scientists and Medichem Research Inc., under Sarawak Medichem Pharmaceuticals Inc. joint venture.	None involving China and India.
15(7)	Fair and equitable sharing of research results & benefits from utilisation of genetic resources.	Joint research and 50:50 stake in intellectual property under joint venture.	Payments to Indian and Chinese suppliers of natural Camptothecin.
16	Access to and transfer of technology.	NCI transfer of screens to Sarawak under Letter of Collection; access by Sarawak scientists to Medichem Research Inc.’s technology under joint venture.	None involving China and India.
18(1)	Technical and scientific co-operation over conservation and sustainable use.	University of Illinois and Sarawak Forestry Department cooperation on sustainable harvesting of <i>Calophyllum teysmannii</i> .	None involving China and India.
18(4)	Co-operative development & use of technology; training and exchange of experts.	Training of Sarawak scientist in isolation techniques at NCI labs under Letter of Collection agreement; training of Sarawak scientists at Medichem Research Inc. under joint venture.	None involving China and India.
18(5)	Joint research programmes and joint ventures for technological development.	Sarawak Medichem Pharmaceuticals Inc. joint venture.	None involving China and India.
19(1)	Source country participation in biotechnological research.	Training and involvement of Sarawak scientists in preclinical and clinical work under joint venture.	None directly involving China and India. These countries now have their own research & development programmes using Camptothecin.
19(2)	Fair and equitable sharing of the results and benefits of biotechnological research.	Joint research and 50:50 stake in intellectual property under joint venture.	Payments to Chinese and Indian suppliers of natural Camptothecin.

A SUMMARY OF THE NATIONAL CANCER INSTITUTE'S POLICY ON ACCESS AND BENEFIT-SHARING

The National Cancer Institute (NCI) is one of the seventeen U.S. National Institutes of Health (NIH) under the auspices of the Department of Health and Human Services of the United States Government. The NCI was established in 1937, with the mission “to provide for, foster and aid in co-ordinating research related to cancer”.¹⁹ Within the Institute, drug discovery and preclinical development is now undertaken by the ‘Developmental Therapeutics Programme’²⁰, a component of the NCI’s Division of Cancer Treatment and Diagnosis.

Over the past forty years, the NCI has facilitated the preclinical anti-tumour screening of more than 400,000 compounds and materials submitted by a wide range of grantees, contractors, pharmaceutical and chemical companies, and other private and public scientific institutions world-wide.

NCI’S COLLABORATIVE APPROACH TO DRUG DEVELOPMENT

Since its inception, the NCI has adopted a collaborative approach to drug development. The NCI uses U.S. government funding to source, screen and isolate natural and synthetic compounds, both through internal research programmes and through collaborative partnerships with academia, the private sector, and other public research organisations. As a government-funded, non-profit organisation, the NCI’s mandate does not allow it to engage in the commercialisation of any of its products, although it may participate in the drug development process through preclinical and clinical studies up to the point of commercialisation. Given this constraint on its activities, the NCI looks to its partnerships with companies to enable the commercialisation process. If, however, products that have been developed by the NCI are not selected for commercialisation by the private sector, the NCI will provide them to the public free of charge if it considers that they are of significant therapeutic value.²¹

The NCI enters into different types of collaborative relationships with its various partners. The structure of these relationships varies according to the purposes that they are intended to serve. The NCI has developed four sets of mechanisms for arranging collaboration with its partners in drug development:

- **Co-operative Research and Development Agreements (CRADAs);**
- **National Co-operative Drug Development Groups (NCDDGs);**
- **the Small Business Innovative Research (SBIR) Grants Programme; and**
- **the NCI Liaison Office Exchange Programme (for clinical trials).**

Each of these types of mechanism is explained in more detail in the Annexe to this paper.

¹⁹ Cragg et al., *Drug Discovery and Development at the United States National Cancer Institute. International Collaboration in Search of New Drugs from Natural Sources*. 1994.

²⁰ For more information on the Developmental Therapeutics Programme (DTP) see <<http://epnws1.ncicrf.gov:2345/dis3d/dtp.html>>.

²¹ Personal communication, Dr Gordon Cragg, National Cancer Institute, 9 February 1998.

SOURCING OF GENETIC RESOURCES FOR THE NCI'S RESEARCH

In 1960, the NCI signed an Interagency Agreement with the United States Department for Agriculture (USDA) under which the Department, with the assistance of its collectors, collecting in source countries, supplied the NCI with plant material for anti-tumour screening. However, the agreement was terminated in 1982 and no further collecting work was done for about four years. This was due to a disappointing rate of success in finding plants containing active lead compounds. However, subsequent new developments, including mechanism-based screening, helped to rekindle the NCI's interest in natural products. In 1986, three five-year contracts were awarded for the collection of plants in tropical and subtropical regions world-wide, at a total cost of \$2.7 million, to the Missouri Botanical Garden (MBG) (collecting in Africa), the New York Botanical Garden (NYBG) (collecting in Central and South America) and the University of Illinois at Chicago (UIC), assisted by the Arnold Arboretum and the Bishop Museum in Honolulu (collecting in South-East Asia). Under these collection contracts, the contractors were obliged to obtain the necessary authorisation from source countries prior to collection work.²²

The collection contracts with the MBG, the NYBG and the UIC were extended for a further 5 years in September 1991, at a total cost of \$3.8 million.²³ Soon after the collection contracts were first issued in 1986, however, the collection contractors began to report that the host countries where they were operating on the NCI's behalf were increasingly reluctant to grant access to their genetic resources. These countries were aware that the samples they were providing were being used for drug development activities and they wished to establish agreements to safeguard their rights in the event of commercialisation before granting the necessary collecting permits.²⁴

In response to the expectations of these source countries, the NCI developed a standard agreement which it could use as a basis for negotiation on the terms of access. The purpose of a model agreement was to capture in legal terms the respective rights and obligations of the NCI, its contract collector and the source country from where materials were being collected.

The first such prototype agreement to be used by the NCI was constructed in the form of a "Letter of Intent" agreement. Developed in 1988, the model Letter of Intent was used as the basis for a binding legal agreement between the NCI and the government of Madagascar in 1990.

By 1992, the NCI had decided that the standard Letter of Intent, although it had undergone revision, was not adequate for the evolving character of its partnerships with source countries and source country organisations. A new prototype agreement, this time in the form of a "Letter of Collection" agreement, was adopted for use in negotiating terms with source country partners.

A third standard agreement, designed as a "Memorandum of Understanding", was introduced by the NCI in 1995, and has increasingly replaced the Letter of Collection as the mechanism for defining partnerships between the NCI and organisations in source countries.

These three prototype agreements, each containing standard terms for use in discussing collaboration with source countries, have been used in turn by the NCI to establish the terms under which the NCI obtains access to genetic resources.²⁵

²² Personal communication, Dr Gordon Cragg, National Cancer Institute, 9 February 1998.

²³ Developmental Therapeutics Program, National Cancer Institute: Undated information document on the Developmental Therapeutics Program (DTP), Division of Cancer Treatment (DCT), National Cancer Institute (NCI).

²⁴ Personal communication, Dr Gordon Cragg, National Cancer Institute, 9 February 1998.

²⁵ For more detail on the differences between the non-benefit sharing provisions of these agreements, please see the Annexe.

MECHANISMS FOR SHARING BENEFITS WITH SOURCE COUNTRIES

All three of the NCI's standard agreements contain terms relating to the sharing of both monetary and non-monetary benefits, although each successive model has placed greater emphasis than its predecessor on commitments to technology transfer, collaborative research and value addition in the source country. Each of the three prototype agreements contains provisions addressing:

- intellectual property rights (involving the payment of royalties and possibilities for joint ownership of patents);
- technology transfer, training and capacity building (involving the training of source country scientists in NCI laboratories);
- confidentiality of ethnobotanical data, including prior informed consent from traditional healers prior to publication and adequate acknowledgement of their contributions;
- joint research;
- the communication of research results to source country institutions;
- resupply (collaboration over the resupply of additional material for discovery, development and scale-up for manufacture); and
- obligations on third party licensees to share benefits with the source country.

Within these common parameters, however, the NCI's standard benefit-sharing terms have evolved considerably from the provisions of the original model Letter of Intent to those contained in the present-day model Memorandum of Understanding. Among others, there have been changes in the degree of research collaboration contemplated between the NCI and the source country, the number of non-monetary benefits such as technology transfer offered to the source country, the role of source countries in negotiating benefits arising out of commercialisation, the scope of the benefits to be shared, and the contracting parties involved.

THE NCI LETTER OF INTENT

The Letter of Intent, the NCI's first standard agreement, was designed to be negotiated and signed between the NCI and a source country, with a separate collection agreement signed between the NCI and a designated collection contractor. There was relatively little provision for collaboration between the NCI and the source country. Other than royalty payments, the main benefits offered to a source country providing samples to the NCI under the terms of the agreement were limited to the training of scientists at the NCI's facilities in the United States and the sharing of the results of research on the samples provided. Any research results were to be communicated indirectly to the source country through the NCI contractor who had initially collected the samples. The Letter of Intent contained no further commitments to involving the source country, or an organisation within the source country, in the product discovery and development process.

The Letter of Intent contained terms providing for the commercialisation of products derived from samples provided to the NCI. With the objective of compensating source countries whose samples were so used, the Letter of Intent provided that, following consultation with the source countries concerned, the NCI would make its "best efforts"²⁶ to negotiate rates of compensation with third party licensees of the NCI's patents on such products. Thus, under its Letter of Intent agreements, the NCI encouraged, but did not require, third party licensees to provide an adequate share in royalties and other benefits.

²⁶ The Letter of Intent stated that: "NCI [would make] its best effort to ensure that royalties and other forms of compensation [are] provided to the host country organisation and to individuals of that country, as appropriate, in an amount ... negotiated with NCI in consultation with the host country organisation." See the preamble to the NCI's model Letter of Intent. Letter of Intent reproduced in Adams, R.P. et al (ed.s), *Conservation of Plant Genes II: Utilization of ancient and modern DNA*. Missouri Botanical Garden, 1994.

THE NCI LETTER OF COLLECTION

In response to constructive criticism from source countries seeking greater involvement in research and in the commercialisation process, the terms of the second model agreement developed by the NCI, the Letter of Collection agreement, reflected a significant evolution from the approach to benefit-sharing taken in its first standard agreement, the Letter of Intent.²⁷ Where the Letter of Intent was effectively a supply agreement, the Letter of Collection provided a contractual framework for more “value-added” collaboration between the NCI and an organisation within a partner source country. The terms of the Letter of Collection provided for the transfer of screening and isolation capabilities from the NCI to the source country organisation, and presented the option of collaboration between the NCI and the source country on the preclinical development of promising drug candidates.

Despite the new emphasis on technology transfer and increased collaboration, however, the terms of the Letter of Collection did not specify when, in the discovery and development process, the screening and isolation capabilities would be developed in the source country or at what point in the collaboration information know-how and technology would be transferred. With the exception of the collaboration in preclinical studies and certain opportunities to work in NCI laboratories or to use “technology...useful in furthering work under [the] agreement”,²⁸ it is unclear whether the benefits offered by the NCI under the terms of the Letter of Collection would support immediate work on agents selected from source country genetic resources, or general capacity-building in the longer term. Thus, despite an increased commitment to collaboration, the presumption remained in the Letter of Collection, as in the Letter of Intent, that the source country would have little direct participation in the discovery and development of the drug candidates in question.

Another significant development in the provisions of the Letter of Collection, by comparison with the Letter of Intent, is that source countries were given an explicit role in the negotiation of the sharing of benefits arising in the event of commercialisation. The unilateral “best efforts”²⁹ undertaking by the NCI contained in the Letter of Intent was unsatisfactory to source country partners seeking greater involvement in the determination of benefits, and the NCI’s ability to enter into benefit-sharing commitments was increasingly constrained by the legal framework which provided it with the statutory authority needed to enter into partnerships of this kind.³⁰ In response, the NCI adopted a new approach in its Letter of Collection agreement. Where the Letter of Intent had given the NCI the power to negotiate, on behalf of the source country, the monetary terms of any license between a licensee company and the source country, the Letter of Collection removed the NCI from the negotiation process. Under the terms of the Letter of Collection, if a private sector organisation indicated that it was interested in obtaining a license for commercialisation of genetic resources provided to the NCI under the agreement, the NCI was obligated to require potential licensees to enter into negotiations on commercialisation directly with source countries.³¹

A third evolution of the Letter of Collection from the Letter of Intent was in the scope of the genetic resources and derivatives to which benefit-sharing obligations attached. The scope under the Letter of Collection was more broadly defined than under the Letter of Intent, covering actual isolates of the natural product, synthetic compounds for which the isolate was a developmental lead, and any associated methods and uses.

²⁷ Personal communication, Dr Gordon Cragg, National Cancer Institute, 9 February 1998.

²⁸ Article 4, model Letter of Collection.

²⁹ Personal communication, Dr Gordon Cragg, National Cancer Institute, 9 February 1998.

³⁰ For a more detailed explanation, see the ‘summary of the legal context for access to genetic resources by the NCI and its practice in benefit-sharing’ in the next section.

³¹ Article 8 of the NCI’s model Letter of Collection states: “*should an agent ...be licensed to a pharmaceutical company for production and marketing, DTP/NCI will require the successful licensee to negotiate and enter into agreement(s) with the appropriate Source Country Government...agency(ies) or Source Country Organisation(s)...This agreement will address the concern on the part of the Source Country Government...or Source Country Organisation(s) that pertinent agencies, institutions and/or persons receive royalties and other forms of compensation as appropriate.*” See <http://www-otd.nci.nih.gov/loc.htm>.

THE NCI MEMORANDUM OF UNDERSTANDING

The latest standard agreement developed by the NCI, its Memorandum of Understanding, is designed to be negotiated directly between the NCI and an organisation in the source country. The Memorandum of Understanding has been developed in response to the increase in the capacities of source countries to engage in drug discovery and development, which has given rise to better opportunities for joint collaboration between the NCI and source country partners. These developments are reflected in the benefit-sharing arrangements contained in the model Memorandum of Understanding, which provides for far greater value-added source country participation in the NCI's research than did either of the two earlier standard agreements.

To begin with, the model Memorandum of Understanding provides for all collection work to be undertaken by an organisation within the source country, rather than by an NCI contractor under a separate agreement, as was the case with both the Letter of Intent and the Letter of Collection. The agreement also provides for greater participation by local source country screening facilities in the screening and fractionation phase of the development process than the Letter of Collection did, and more emphasis is given to utilising existing source country capabilities. Where these are lacking, the Memorandum of Understanding provides that the NCI will equip the source country with cell lines and appropriate bio-assays, subject to available resources, not only as part of a general commitment to capacity building, but for the specific purposes of furthering work on anti-cancer and anti-HIV therapeutics under the agreement itself. Some aspects of source country involvement in research is not specified in the Memorandum of Understanding itself, but may take place in practice, if mutually agreed between NCI and the source country during the collaboration. For example, one or more of the phases of preclinical development may be conducted in the source country, if source country institutions possess the relevant expertise and capacity. Secondly, if a compound isolated by a source country organisation merits advancement into preclinical development, the source country organisation may elect to apply for patent protection on the compound using data from the NCI preclinical trials. The NCI data is considered routine, so the NCI makes no claim to co-inventorship, thus giving the source country organisation sole ownership over the invention.³²

As in the Letter of Collection, the Memorandum of Understanding provides that source countries will enter into direct negotiations with potential licensees. The Memorandum of Understanding progresses a step further, however, by providing that the NCI will not distribute materials provided by the source country to other organisations without written authorisation from the source country. This requirement for source country consent to transfer reflects the new joint responsibility between the NCI and the source country in co-ordinating drug discovery and development envisaged by the Memorandum of Understanding.

The Memorandum of Understanding also contains more specific terms for the repatriation of test results to the Source Country than does the Letter of Collection.³³

Although it currently uses both types of agreement, the NCI is hoping to increase the proportion of partnerships with source countries made under the more collaborative terms of its standard Memorandum of Understanding, compared to those made under the Letter of Collection.

Further information on the NCI and the terms of the three standard NCI agreements is contained in the Annexe to this paper.

³² Personal communication, Dr Gordon Cragg, National Cancer Institute, 17 April, 1998.

³³ Rather than stating that results should be returned quarterly, as in the Letter of Collection, the NCI's model Memorandum of Understanding provides for the repatriation of *in vitro* results within a 90 days. An absolute limit of 270 days is laid down and any further delays must be explained in writing to the source country. Article 5 of the NCI's model Memorandum of Understanding. Copy obtained in correspondence from Dr. Rita Khanna, National Cancer Institute, 9 February 1998.

A SUMMARY OF THE LEGAL CONTEXT FOR ACCESS TO GENETIC RESOURCES BY THE NCI AND ITS PRACTICE IN BENEFIT-SHARING

A number of laws provide the framework within which the NCI is obliged to operate. These both enable and constrain its ability to share benefits, since U.S. Federal government agencies are empowered to act by statutory authority. If no explicit statutory authority exists, an agency generally may not engage in a particular activity.³⁴

As a Federal agency of the U.S. government, the NCI must therefore ensure that it is authorised to conduct each of the activities that are involved in access and benefit-sharing. These could typically include collecting genetic resources itself, retaining agents to do so on its behalf, establishing laboratories or other scientific facilities, conducting research and development activities, conducting clinical trials or submitting drug candidates for clinical trials by others, and transferring technology and licensing products to other organisations. If the NCI is to engage in any such activities, it must have the explicit legal authority to enter into the legally binding agreements with the various partners involved which are necessary to clarify respective rights and responsibilities. The statutory authority must allow the NCI to make any necessary payments to its partners for their services or to receive payment from them in return for services rendered by the NCI itself. The following paragraphs explore the manner in which the current U.S. legal framework both enables and restricts the ability of the NCI to enter into access and benefit-sharing arrangements.

One constraint on the NCI's ability to enter into such arrangements lies in the provisions of the statutes which authorise its activities in the field of commercialisation. In common with other U.S. Federal agencies, the NCI is not permitted to engage in profit-making ventures, and is specifically prohibited from competing with private sector organisations.³⁵ Two U.S. statutes, in particular, empower the NCI to engage in activities central to drug development, but which fall short of direct commercialisation by the NCI itself. One statute, 35 USC 207, enables the U.S. government to patent and license inventions that arise from federal laboratories.³⁶ This statute stipulates exactly how a federal laboratory such as the NCI may patent, and offer an exclusive license on, the results of its work. A second statute, the U.S. Federal Technology Transfer Act of 1986 (FTTA),³⁷ empowers a federal laboratory such as the NCI to enter into 'Cooperative Research And Development Agreements' (CRADAs) with private sector organisations such as companies, and to license its inventions to private sector partners.

The circumstances in which each of these two approaches would be appropriate are as follows. A license under 35 USC 207 would be likely to be used where NCI had demonstrated an invention through work in its laboratories, but needed to enter into partnership with a private sector company in order to market the drug to the public. Since taxpayers' funds had supported the development of this invention, public policy would require open competition among potential licensees, based on the notice provision in the statute.³⁸

³⁴ U.S. Federal government agencies operate under specific statutory authority. However, under U.S. administrative law, Federal agencies do have some discretion to act, provided they do so in a manner that is not inconsistent with specific statutory authority. Personal communication, Mr. Tom Mays, Morrison & Foerster (formerly of the National Cancer Institute), 17 April 1998.

³⁵ Several statutory prescriptions have this effect. For example, paragraph 5 of 15 USC 3710c is a direction to Federal laboratories to establish an office of technology transfer, and stipulates that no such office of research and technology applications nor other organisational structure performing the functions prescribed for it shall compete with similar services available in the private sector. Personal communication, Mr. Tom Mays, Morrison & Foerster, 17 April 1998.

³⁶ 35 USC 207. Another, similar, piece of legislation, 35 USC 202, applies to universities and other bodies that receive federal funding.

³⁷ 15 USC 3710a.

³⁸ Among the procedural steps prescribed by the statute are the need for the NCI to give notice in the U.S. Federal Register of the availability of a compound or drug for licensing; to consider applications submitted by potential licensees; to select an applicant from among them based on certain criteria; and to post notice of its intent to license the compound or drug to the chosen applicant for a period of ninety days, during which the public may comment on the proposed license. Only once these steps have been fulfilled may the NCI grant

Where the development of the drug would require further improvements of the product, a CRADA would be more appropriate. In this case, where the private sector partner invests time and money to help the Federal agency involved, public policy allows the commercial partner involved in the CRADA to obtain a license on the invention that arises under that agreement in a preferential way, without open competition, and without providing notice in the Federal Register.³⁹

Both statutes contain similar preferential provisions which require U.S. Federal agencies to give 'preference' to two categories of licensee: U.S.-based institutions and small businesses.⁴⁰ Consequently, source country organisations would need to compete with other potential licensees. U.S. companies and small businesses are therefore more likely to succeed than a source country organisation, unless it is more qualified than any other candidate.

Thus, statutory provisions on notice procedures, requirements for competition and preferences for certain categories of licensee which apply when the NCI licenses its inventions under either of these two authorising statutes lie behind the NCI's dilemma concerning benefit-sharing: how can it make specific benefit-sharing commitments to source countries in return for access to their genetic resources when the only mechanism to commercialise results and obtain monetary benefits to share requires open competition that 'prefers' US-based licensees?

The second factor constraining the NCI's ability to commit to benefit-sharing arises from the fact that the statutory authority for the NCI to pay its partners, including source countries, is strictly limited. When a source country organisation has offered a service, for example the conduct of research leading to an invention, then and only then can the NCI pay that organisation. In the case of a joint patent, where a source country organisation has contributed to the inventive step, the source country organisation is entitled to a share in royalties on the sales arising from any licenses of the invention and to inventorship, determined on the basis of U.S. law.⁴¹ It is currently questionable, however, whether the granting of access to genetic resources alone would constitute services such that the NCI would be authorised to pay a fee for access or justify a royalty payment.⁴² For this reason, NCI has adopted the alternative method of ensuring that benefits are shared, as described below.

A third constraint upon the NCI's ability to commit to share benefits with source country organisations exists in circumstances where the NCI contracts with universities or other institutions for them to conduct research that is paid for by federal funds. In these circumstances, another U.S. federal statute provides that the contractor is entitled to retain ownership over any intellectual property it creates as a result of the

the license. Since exclusive licenses are generally of more interest to pharmaceutical companies, for whom exclusivity is often the key to competitiveness, this is the route generally pursued by the NCI. Should the NCI wish to offer a non-exclusive license, the statute does not require notice in the Federal Register, although the same procedure is generally followed anyway, as it is an opportunity to advertise the availability of the compound to potential licensees. Personal communication, Mr. Tom Mays, Morrison & Foerster, 9 April 1998.

³⁹ Personal communication, Mr. Tom Mays, Morrison & Foerster, 17 April 1998.

⁴⁰ 15 USC 3710a requires a preference or special consideration for US-based companies, or foreign companies with substantial manufacturing activities in the USA, and for small businesses. 35 USC 207 contains a similar 'preference' provision, in favour of companies based in the U.S. or whose products are manufactured substantially in the U.S..

⁴¹ Application of the inventorship test under U.S. patent law does not allow an individual or institution to be a named co-author on a patent unless it has contributed to the inventive step. "'Inventor' is a legal term in U.S. patent law, and the naming of inventors on a given patent usually requires the determination of 'inventorship' by appropriate legal experts. An incorrect designation of invention(s) can completely void a patent, and also may result in legal liability for any intentional misrepresentation." (Boyd, Michael R., "The Position of Intellectual Property Rights in Drug Discovery and Development from Natural Products", draft paper for *J. Ethnopharmacology*, presented at Symposium on "Intellectual Property Rights, Naturally Derived Bioactive Compounds and Resource Conservation", San Jose, Costa Rica, October 20-22, 1994.) Therefore, unless a source country organisation has participated to a standard that would satisfy U.S. legal experts, it will be impossible to share in the long-term benefits of inventorship, such as royalties.

⁴² To date, the NCI has awarded its contract collectors a set sum, based on the number of samples the contractor provides to the NCI, and on the basis of competitive bids by potential contract collectors. Contract collectors are required by NCI to abide by all relevant legislation as they conduct their collections. If a fee is required for access to genetic resources, the contract collector would pay the relevant sum out of the set sum it received. Any request for a higher grant in order to pay for access fees might have made a collector uncompetitive. However, if the payment of up-front fees for access become a common requirement of access legislation around the world, contract collectors could demonstrate that benefit-sharing in this way was a requirement for them to satisfy their obligations under the contract with NCI to abide by all relevant laws in the countries where they collect. Personal communication, Dr. Gordon Cragg, National Cancer Institute and Mr. Tom Mays, Morrison & Foerster, 17 April 1998.

research and to commercialise the results on its own terms.⁴³ Under this statute, a contractor could legally choose to do so without sharing benefits with the country from where the genetic resources upon which the invention is derived were provided to the NCI. To resolve this problem, however, the NCI requires all third party university or other recipient institutions to sign a legally binding material transfer agreement (the NCI MTA) before granting them access to its repository of materials or extracts derived from organisms collected through collection in source countries. This agreement informs the recipient of the rights of the source countries, and obliges the recipient to negotiate benefit-sharing directly with the source countries, in the same fashion as described above with respect to the NCI Letter of Collection agreement.⁴⁴

In summary, the ability of the NCI to enter into legally binding commitments with source countries to share the benefits arising from the commercialisation of products derived from their genetic resources is very limited. Since the NCI is obliged to act within a legal framework which, in some important respects, does not help it to share benefits, it has developed the solution described in the preceding section: namely, the Letter of Collection and the Memorandum of Understanding. These standard agreements contain commitments to source countries to apprise potential licensees of the existence of the agreements.⁴⁵ Also, clauses in the NCI's CRADAs, licenses and MTAs oblige recipients of genetic resources to negotiate and enter into agreement(s) directly with the source country.

THE CASE OF CALANOLIDE

LEGAL AND POLICY CONTEXTS

LAW AND POLICY ON ACCESS AND BENEFIT-SHARING IN MALAYSIA AT THE TIME *CALOPHYLLUM* WAS COLLECTED

Peninsular Malaysia

Malaysia's National Conservation Strategy of 1993, commissioned by the Economic Planning Unit of the Prime Minister's Department, contains a number of recommendations for the development of a comprehensive strategy for the conservation of Malaysian biodiversity. It lists biodiversity prospecting as a priority activity with the objective of optimising "economic benefits from sustainable utilisation of the components of biological diversity".⁴⁶

Malaysia comprises thirteen States, each with its own legislature. The powers of each State, defined by the Federal Constitution, depend upon whether a particular issue is found on the Federal List, in which case it falls within the jurisdiction of central government, the State List, which sets out matters within the competence of each State, and the Concurrent List, which details issues for which States and central government share competence. 'Biological diversity' itself is not found on any of the lists, but certain aspects of it are found on each of the three lists. Other aspects are not addressed on any list. For example, matters related to land and natural Resources, including forests and water, are found on the State List, and lie within the exclusive jurisdiction of each State. Marine fisheries are on the Federal list, while

⁴³ Bayh-Dole Act, 1980: 35 USC 201 *et seq.*

⁴⁴ Personal communication, Dr. Gordon Cragg, National Cancer Institute, 17 April 1998.

⁴⁵ See Article 7, Letter of Collection, and Article 11, Letter of Intent.

⁴⁶ Mullard, Sally. 1998. "Review of the Status of Access and Benefit-Sharing Measures in Malaysia". WWF Briefing Paper based on Oh, Cecilia. 1997. In *Harvesting the Green Gold: A Review of the Policy and Legal Framework for Access and Benefit-Sharing in Malaysia*. WWF Discussion Paper.

jurisdiction over wildlife is shared between central government and the States, as wildlife protection appears on the Concurrent List.⁴⁷

There is no legislation directly addressing access to genetic resources, commercialisation, or benefit-sharing in Malaysia. Rather, provisions in the National Forestry Act 1984, the Protection of Wildlife Act 1972 and the Fisheries Act 1985 contain the majority of provisions relevant to access to genetic Resources in Peninsular Malaysia.

The Economic Planning Unit of the Prime Minister's Department currently administers a system of research permits for Peninsular Malaysia,⁴⁸ requiring foreigners wishing to conduct research in Malaysia to "obtain permission from the Government of Malaysia to do so and to obtain the necessary visa for conducting research". The Customs and Excise and Plant Quarantine Departments control export permits. Various authorities such as the Fisheries Department and the Ministry of Science, Technology and the Environment (MOSTE) manage sectoral and conservation issues.

Sabah and Sarawak

The States of Sabah and Sarawak have their own laws on forests and the protection of wildlife.

The *Calophyllum* experience in Sarawak

Although the UIC's first 1987 collections in Sarawak were authorised with a permit for collection and export by the Economic Planning Unit of the Prime Minister's Department in Kuala Lumpur, a second permit was issued by the Sarawak Forestry Department in Kuching. The Department again provided permission for the UIC's survey work on *Calophyllum* species starting in March 1992. With proposals for longer field surveys in 1992 after the activity of *C. teysmannii* was discovered earlier that year, the NCI's Letter of Collection was first presented to the Forestry Department leading to negotiations with the Sarawak Government. Meanwhile, an application for a research permit had to be submitted to the Sarawak Secretary of State. The Sarawak State Secretary eventually signed the Letter of Collection in June 1994.⁴⁹

Recent developments

In 1994, in the light of the *Calophyllum* case, Sarawak amended its Forests Ordinance to include specific clauses on access to genetic resources. The provisions of the amendment state that, prior to removing or exporting trees or any of their derivatives in order to conduct research for the purposes of developing pharmaceutical or medicinal compounds, an individual must obtain the authorisation of the Director of Forests, as approved by the Minister.⁵⁰ The amendment, however, covers tree species alone, restricts only those commercial uses that are related to healthcare, and is open to the possible interpretation that applicants for access who did not, at the time of access, intend to develop pharmaceutical or medicinal products, but subsequently decided to do so, would not be bound by its provisions.

⁴⁷ Mullard, Sally. 1998. *Review of the Status of Access and Benefit-Sharing Measures in Malaysia*. WWF Briefing Paper based on Oh, Cecilia. 1997. In "Harvesting the Green Gold: A Review of the Policy and Legal Framework for Access and Benefit-Sharing in Malaysia." WWF Discussion Paper.

⁴⁸ Economic Planning Unit, 1993. *Procedures for Conducting Research in Malaysia*. Prime Minister's Department, Kuala Lumpur, Malaysia, as cited in Mullard, 1998.

⁴⁹ Personal communication, Dr Gordon Cragg, National Cancer Institute, 3 March 1998.

⁵⁰ Forests Ordinance, April 1994. Section 65A states that "... no person shall, without the written authorisation granted by the Director [of Forests] with the approval of the Minister ... (a) cut, remove or take any tree found in any State land or in any forest reserve, protected or communal forest for undertaking or conducting any research, study, experiment, process or test in relation to the production or development or intended production or development of any pharmaceutical product or medicinal compound; and (b) take out, export or repatriate from the State of Sarawak any tree or any compound, extract, by-product, sample or tissue of any tree for use in any research, study, experiment process or test in connection with the production or development of any pharmaceutical product or medicinal compound or intended production or development thereof."

CURRENT DEVELOPMENTS ON ACCESS TO GENETIC RESOURCES IN MALAYSIA

Peninsular Malaysia

Two possible approaches are under consideration for the revision of the law governing access to genetic resources in Malaysia. Either new, national legislation could be introduced as a framework governing access to genetic resources in all the Malaysian States, or amendments could be made to the various provisions currently in force in Peninsular Malaysia, Sabah and Sarawak. Since many aspects of regulating access to genetic resources are under State jurisdiction, the Federal Government is not, at a first glance, in a position to enact framework legislation. The Constitution does provide, however, for a legislative role to fulfil obligations under international treaties and to promote uniformity of laws between two or more States, although each State must adopt its own implementing legislation in this case. However, the political feasibility of States agreeing to adopt new legislation is questionable. In 1997, the Attorney-General's Chambers took the view that the constitutional position in Malaysia would make a general, all-encompassing Act impossible to implement.

Thus the Attorney-General's Chambers proposed the introduction of an Access Licensing System through the amendment of the three existing Acts. Similar amendments to each Act would require researchers to obtain a license prior to conducting "all activities relating to prospecting, collection, research, utilisation and development of genetic resources". While this would introduce a requirement for prior informed consent, observers have drawn attention to important limitations to this approach, such as the exclusion of plants and microbial genetic resources from the scope of the legislation, its applicability only to foreigners and not to nationals, and the limited geographical coverage of Peninsular Malaysia and not Sabah or Sarawak.⁵¹ The Malaysian government, through its Task Force on Access to Genetic Resources, is now reconsidering the more all-embracing approach to regulation of access.

Sarawak

A new Sarawak Biodiversity Centre Ordinance came in to effect on 1 January 1998, and introduces a new regime for the regulation of access to genetic resources in Sarawak. The Sarawak Biodiversity Centre will act as a focal point for biodiversity and access issues, and will be governed by the Sarawak Biodiversity Council. This body will regulate "the access, collection, study and research, experiment, protection and utilisation of the biodiversity of Sarawak, including the removal of any of the biodiversity from the State". Collectors and researchers must apply to the Centre for a permit, and the smuggling of genetic resources is punishable by a fine of several thousand dollars or imprisonment for three years or both. The Centre will produce an inventory of Sarawak's biodiversity, run programmes on its conservation and sustainable utilisation, and promote public education and awareness raising. It is also responsible for monitoring and enforcing the Ordinance.

OBJECTIVES

Consistent with its mandate and policies, described in the Appendix, the objective of the NCI in entering into partnership with Medichem Research Incorporated and the State Government of Sarawak, was to facilitate the discovery, development and availability of a new anti-AIDS drug from a natural product.

⁵¹ Personal notes from Genting Highlands Workshop on Access to Genetic Resources, Malaysia, August 1997, and Mullard, Sally, 1998, *supra*.

Medichem Research is a private biotechnology firm based at Lemont, Illinois, USA, which specialises in organic synthesis for application to drug discovery and development. Its 58 scientists conduct proprietary and contract research for customers including 500 pharmaceutical and biotechnology companies in the US, and companies in Western Europe. In addition to an anti-AIDS drug, it holds patents on synthetic compounds active against adult respiratory distress syndrome and an anti-viral agent effective against hepatitis B and influenza. Its objective in entering into the partnership with the State government of Sarawak and the NCI was to gain access to a novel compound, and develop it into a marketable drug.

The State Government of Sarawak wishes to build the capacity of Sarawak scientists to develop useful products from Sarawak genetic resources, thus promoting sustainable economic development and contributing to the conservation of Sarawak's biodiversity. Its objective in entering into partnership with the NCI and Medichem Research Inc. was to gain access to technology, training and a stake in the development of any pharmaceutical product derived from Sarawak's genetic resources, through financial partnerships and collaborative scientific research.

CONTENT AND IMPLEMENTATION OF THE ARRANGEMENTS

INPUTS

Initial collections of the twigs and leaves of *Calophyllum lanigerum* were carried out in 1987 by botanists from the Sarawak State Forestry Department in collaboration with John Burley, a research associate of the University of Illinois at Chicago (UIC)⁵². The UIC's participation in collecting expeditions between 1986 and 1991 was under the auspices of the Southeast Asian Plant Collection Contract between the NCI and the UIC. The UIC obtained a collection and export permit from the Prime Minister's Department in Kuala Lumpur, as well as a permit from the Sarawak Forestry Department.⁵³ However, there was no formal agreement between the NCI and the Sarawak Government at this time, given that the NCI's Letter of Intent (Letter of Intent) was developed only in 1988.⁵⁴

The NCI screened solvent extracts of *C. lanigerum*. This revealed significant *in vitro* anti-HIV activity, leading the Institute's Drug Discovery Research and Development Laboratory to Isolate a novel compound of the coumarin class, (+)-Calanolide A.⁵⁵ Along with other Calanolide compounds, (+)-Calanolide A suppresses the *in vitro* replication of HIV-1 and several resistant mutations of that virus. Activity against HIV-1 mutants is especially significant since other drugs, such as AZT, are unable to control them. Potential for using Calanolides in combination with AZT has therefore been recognised⁵⁶ as an important means of suppressing retroviral replication,⁵⁷ and Calanolides are now classified as one of the class of anti-AIDS drugs known as non-nucleoside reverse transcriptase inhibitors (NNRTIs), with an interesting and apparently unique mechanism for inhibiting the activity of the transcriptase enzyme.^{58,59}

In 1991, the NCI renewed its Collection Contract with the UIC to cover work up to and including 1996. Early in the same year and with further funding from the NCI, the Sarawak Forestry Department and Dr David Frodin (a project consultant) attempted to relocate the original *C. lanigerum* tree and find other

⁵² Personal communication, Dr David Frodin, RBG Kew, and Prof. Doel Soejarto, University of Illinois at Chicago, 9 March 1998.

⁵³ Personal communication, Prof. Doel Soejarto, College of Pharmacy, University of Illinois at Chicago, 9 March 1998.

⁵⁴ Personal communication, Dr Gordon Cragg, National Cancer Institute, 9 February 1998.

⁵⁵ Mays, T. D., K. D. Mazan, G. Cragg, M. Boyd, *A paradigm for the Equitable Sharing of Benefits Resulting from Biodiversity Research and Development*, in Grifo & Rosenthal, "Biodiversity and Human Health", 1997 Island Press.

⁵⁶ Asia Times, Wednesday 12th June 1996.

⁵⁷ Personal communication, Dr Tuah Jenta, Sarawak Medichem, 18 February & 2 March 1998.

⁵⁸ Ibid.

⁵⁹ The Calanolides' mechanism of inhibition avoids a mutation in the transcriptase enzyme which other inhibitors including AZT usually cause. Such a mutation would otherwise interfere in the ability of Calanolides to be fully active against HIV-1. Personal communication, Dr Gordon Cragg, National Cancer Institute, 3 March 1998.

productive specimens of the same species.⁶⁰ However, the original tree had in the meantime been lost⁶¹ and subsequent collections from other individuals did not produce significant quantities of (+)-Calanolide A.⁶² Tests results from these new collections varied, though all demonstrated less activity than the original. It has been suggested that production of the compound is dependent on a number of factors including the immediate growth environment of *C. lanigerum* at the time of harvest.⁶³

In March 1992, Dr Doel Soejarto of the UIC visited Sarawak to investigate these findings further in collaboration with staff of the Sarawak Forest Herbarium and with the permission of the Sarawak Forest Department.⁶⁴ A decision to investigate other *Calophyllum* species was made, and screening and isolation work at the NCI following fieldwork in July of that year revealed that the related species *Calophyllum teysmannii* was found to yield (-)-Calanolide B, very similar to (+)-Calanolide A and a potential alternative for drug development, despite its lower activity.⁶⁵ The advantage of (-)-Calanolide B lies in its high yield from latex⁶⁶, offering interesting possibilities for sustainable harvesting. This finding led to a proposal for a longer-term field survey of this species.⁶⁷ The technique developed by Dr. Soejarto for tapping latex from *Calophyllum teysmannii* by making small slash wounds in the bark of the mature trees without harming them was included in the NCI patent, with Dr. Soejarto names as co-author.⁶⁸

In light of such developments, it was felt that a formal relationship needed to be established between the NCI and the Sarawak Government. Thus on 25th August 1992, the Forestry Department was presented with an NCI Letter of Collection entitled, "Agreement between the Sarawak Forestry Department and the Developmental Therapeutics Program of the Division of Cancer Treatment (NCI)". An application was also made for a research permit from the Sarawak State Secretary. However, whilst negotiations were underway, the Forestry Department decided to continue supporting Phase I of this longer-term survey work.⁶⁹

The Agreement was finally signed by the Sarawak State Secretary in June 1994.⁷⁰ Its modified terms specified the conditions under which the NCI could continue to develop the Calanolides and expressed Sarawak's desire for involvement in collaborative research.⁷¹

Phase II of the Sarawak Forestry Department/ UIC collaborative survey of *Calophyllum teysmannii* began soon after.⁷² This survey investigated the occurrence and abundance of the species,⁷³ as well as its potential for propagation and cultivation.⁷⁴ In August - September 1993, 1 kilogramme of latex was collected and shipped to the NCI for further analysis of (-)-Calanolide B. Larger amounts were requested by the NCI in March 1995.

⁶⁰ Personal communication, Dr David Frodin, RBG Kew, & with Prof. Doel Soejarto, University of Illinois at Chicago, 9 March 1998.

⁶¹ Nature's Pharmacy : <http://www.nwf.org/nwf/endangered/news/>

⁶² Mays, T. D., K. D. Mazan, G. Cragg, M. Boyd, *A paradigm for the Equitable Sharing of Benefits Resulting from Biodiversity Research and Development*, in Grifo & Rosenthal, "Biodiversity and Human Health", 1997 Island Press.

⁶³ Personal communication, Dr David Frodin, RBG Kew, 9 March 1998.

⁶⁴ Personal communication, Prof. Doel Soejarto, College of Pharmacy, University of Illinois at Chicago, 9 March 1998.

⁶⁵ Cragg et al., *Drug Discovery and Development at the United States National Cancer Institute. International Collaboration in search of new drugs from natural sources.* 1994.

⁶⁶ With over 20% content. Mays, T. D., K. D. Mazan, G. Cragg, M. Boyd, *A paradigm for the Equitable Sharing of Benefits Resulting from Biodiversity Research and Development*, in Grifo & Rosenthal, "Biodiversity and Human Health", 1997 Island Press.

⁶⁷ Personal communication, Dr. Doel Soejarto, College of Pharmacy, University of Illinois at Chicago, 9 March 1998.

⁶⁸ Personal communication, Dr. Doel Soejarto, College of Pharmacy, University of Illinois at Chicago, 21 April 1998.

⁶⁹ Personal communication, Dr. Doel Soejarto, College of Pharmacy, University of Illinois at Chicago, 9 March 1998.

⁷⁰ Ibid.

⁷¹ Personal communication, Dr Gordon Cragg, National Cancer Institute, 9 February 1998.

⁷² Cashman et al. *J. Medchem.* 1992, vol. 35, 2735-2743 & Personal communication, Dr. Doel Soejarto, College of Pharmacy, University of Illinois at Chicago, 9 March 1998.

⁷³ Mays, T. D., K. D. Mazan, G. Cragg, M. Boyd, *A paradigm for the Equitable Sharing of Benefits Resulting from Biodiversity Research and Development*, in Grifo & Rosenthal, "Biodiversity and Human Health", 1997 Island Press.

⁷⁴ Cragg et al., *Drug discovery and development at the National Cancer Institute: potential for new pharmaceutical crops.* <http://www.hort.purdue.edu/newcrop/proceedings_1996/>.

Meanwhile, in autumn 1992, the NCI published the structure of (+)-Calanolide A⁷⁵ and selected it for pre-clinical development.⁷⁶ It subsequently filed patents on (+)-Calanolide A and other Calanolides, including (-)-Calanolide B, in 1993 and 1995.⁷⁷ Also in 1993, an NIH Small Business Innovation Research (SIBR) grant was awarded to Medichem Research Incorporated.⁷⁸

In 1995, in light of the achievements under the SIBR, the NCI awarded Medichem Research a world-wide, exclusive license to its patents on the preparation and use of Calanolides.⁷⁹ Medichem Research thereby gained full, exclusive rights to the further preclinical development, clinical trials and commercialisation of (+)-Calanolide A, leaving the NCI to divert its resources elsewhere.⁸⁰ The license specified that Medichem Research was obliged to negotiate an agreement with the Sarawak Government,⁸¹ thus fulfilling the NCI's obligations under the 1994 Letter of Collection agreement.

Medichem Research undertook various product chemical, animal toxicity and animal pharmacokinetic studies of (+)-Calanolide A throughout 1995, 1996 and 1997.⁸² They revealed that (+)-Calanolide A was tolerable *in vivo* at relatively high concentrations and that it appears both to cross the blood-brain barrier and to enter into the lymphatic system. This is important since both the brain and the lymphatic system can be reservoirs for the HIV virus.⁸³ Such findings established the drug as a good candidate for clinical trials in the USA and, to that end, it was submitted for FDA approval as an Investigational New Drug (IND). Soon after, Medichem Research began discussing with the Sarawak Government options for the State's participation in the drug's further development. Negotiations proceeded smoothly over six months, during which time Medichem Research continued to progress with the compound. The outcome of these negotiations was the creation of a joint venture between the State Government of Sarawak and Medichem Research. The joint venture, called Sarawak Medichem Pharmaceuticals Incorporated (SMP), was officially agreed upon by both parties at the end of 1996.

The joint venture effectively encompasses the range of NCI-patented Calanolides to which Medichem Research obtained an exclusive, world-wide license in 1995. The rights attached to that license are therefore held jointly by Medichem Research and the Sarawak Government. Further work on the Calanolides, currently being conducted by SMP, has been facilitated by the signing of a CRADA between the NCI and Medichem Research in 1997. SMP now has the right to file patents on all subsequent innovations arising out of this work. As with rights under the exclusive license, Medichem Research and the Sarawak Government will own such patents jointly.⁸⁴

The joint venture has set out to achieve a number of key goals:

- (1) To bring (+)-Calanolide A (the primary candidate) to clinical development with the objective of obtaining FDA approval as an anti-HIV drug in the U.S.A..
- (2) To develop (-)-Calanolide B (Costatolide) as a candidate for clinical development.
- (3) To facilitate the investigation of other drug candidates from the Malaysian rainforest (as part of Sarawak's approach to sustainable development).

⁷⁵ Personal communication, Dr. Doel Soejarto, College of Pharmacy, University of Illinois at Chicago, 9 March 1998.

⁷⁶ Cragg et al., *The Role of Plants in the Drug Discovery Program of the United States National Cancer Institute*.

⁷⁷ Personal communication, Dr Gordon Cragg, National Cancer Institute, 9 February 1998.

⁷⁸ Personal communication, Dr Tom Flavin, Medichem Research, 18 February 1998.

⁷⁹ Personal communication, Dr Tuah Jenta, Sarawak Medichem, 18 February & 2 March 1998.

⁸⁰ Personal communication, Dr Gordon Cragg, National Cancer Institute, 9 February 1998.

⁸¹ Under Articles 7 and 8 of the Letter of Collection, NCI's policy is for a licensee of an NCI-patented product to be apprised of obligations to source countries under the Letter of Collection concerned and, consequently, to negotiate directly with the source country over adequate compensation, e.g. payment of an adequate share in royalties. Having put the licensee and source country in contact, NCI drops out of the picture. The rationale behind this is that NCI cannot, under US law, bind a licensee to terms agreed between NCI and the source country. Personal communication, Dr Gordon Cragg, National Cancer Institute, 9 February 1998.

⁸² Personal communication, Dr Tuah Jenta, Sarawak Medichem, 18 February & 2 March 1998.

⁸³ Personal communication, Dr Tom Flavin, Medichem Research, 18 February 1998.

⁸⁴ Personal communication, Dr Tuah Jenta, Sarawak Medichem, 18 February & 2 March 1998.

(4) To operate as a platform for the training of Malaysian scientists.⁸⁵

The (+)-Calanolide A Investigational New Drug (IND) application was approved by the FDA in mid 1997⁸⁶. The drug candidate entered Phase IA clinical trials shortly thereafter, during which toxicity was tested in fifty volunteer human patients over a seven-month period in the USA.⁸⁷ These trials demonstrated that (+)-Calanolide A is well tolerated in human subjects.⁸⁸

As (+)-Calanolide A's movement towards commercialisation has progressed, scale-up of the production of the compound has become essential, in order to supply the compound in sufficient quantities for the various pre-clinical and clinical trials. (+)-Calanolide A cannot be sourced in adequate quantities from the wild, so Medichem Research, an expert in the field of synthetic chemistry, needed to find a means of synthetic production of the compound. Initial attempts at synthesis took six to nine months to produce just 2 grammes. The company has, nevertheless, succeeded in reducing the number of stages involved in synthesis, thus increasing both the rate and the quantity of production.⁸⁹ Unfortunately, synthesised batches of racemic -Calanolide A are less active than the naturally occurring compound.⁹⁰

It is hoped that (+)-Calanolide A will reach sick patients in Phase II trials in May - June 1998. The joint venture has also begun investigating other back-up compounds, in case (+)-Calanolide A does not succeed in Phase II and Phase III clinical trials. A Sarawak scientist working with Medichem Research is making an important contribution to the research on back-up compounds.

Meanwhile, (-)-Calanolide B has reached the preclinical stage, with funding from an NIH Small Business & Innovative Research Grants (SBIR) Phase I Grant.⁹¹ However, unlike (+)-Calanolide A, its ease of sourcing from latex has eliminated many potential problems with scale-up for supply for toxicological studies.⁹² To that end, the NCI's request for latex in March 1995 prompted the development of a project, jointly funded by the NCI and the Sarawak Government, and managed by the Forestry Department. A crew of seven tapped over two hundred trees, obtaining 60 kilograms of latex. 50 kilograms were then shipped to the NCI. Since the SMP joint venture was established, Medichem Research, in its capacity as SMP's contractor, processes latex for adequate quantities of (-)-Calanolide B⁹³. 20 kilograms were

⁸⁵ Personal communication, Dr Tuah Jenta, Sarawak Medichem, 18 February & 2 March 1998.

⁸⁶ Personal communication, Dr Tuah Jenta, Sarawak Medichem, 18 February & 2 March 1998.

⁸⁷ Chicago Tribune, Business; Thursday June 19, 1997.

⁸⁸ Personal communication, Dr Tom Flavin, Medichem Research, 18 February 1998.

⁸⁹ Personal communication, Dr Tom Flavin, Medichem Research, 18 February 1998.

⁹⁰ The lower activity of synthesised batches of racemic -Calanolide A is a result of the fact that they contain the (-) enantiomer, (-)-Calanolide A, which is less active than the (+) enantiomer, (+)-Calanolide A.

⁹¹ Personal communication, Dr Tom Flavin, Medichem Research & Dr Tuah Jenta, Sarawak Medichem, 18 February 1998. Personal communication with Dr Tuah Jenta, Sarawak Medichem, 2 March 1998.

⁹² Mays, T. D., K. D. Mazan, G. Cragg, M. Boyd, *A paradigm for the Equitable Sharing of Benefits Resulting from Biodiversity Research and Development*, in Grifo & Rosenthal, "Biodiversity and Human Health", 1997 Island Press.

⁹³ Personal communication, Dr Doel Soejarto, College of Pharmacy, University of Illinois at Chicago, 9 March 1998.

therefore transferred from the NCI repository to Medichem Research in early 1998⁹⁴ and SMP will in the future facilitate further imports of latex from Sarawak with prior approval of the Sarawak Government's Natural Products Research Committee, which consists of senior Sarawak State Government officials.⁹⁵

⁹⁴ Personal communication, Dr Gordon Cragg, National Cancer Institute, 9 February 1998.

⁹⁵ Personal communication, Dr Tuah Jenta, Sarawak Medichem, 2 March 1998.

SUMMARY OF INPUTS & BENEFITS CONCERNING CALANOLIDE

	UIC	NCI	Medichem Research	Sarawak Government	Sarawak Medichem Pharmaceuticals (SMP)
Inputs:	<ul style="list-style-type: none"> Collaborative work with the Sarawak Forest Department: collection of specimens, species surveys & sustainable management of <i>C. teysmannii</i>. Planning, formulation and monitoring of field work. Communication of results to Sarawak counterparts. <i>C. teysmannii</i> var. <i>innophylloide</i> identified during survey in March 1992. 	<ul style="list-style-type: none"> Financial support for the UIC Contract Collections. Screening of collected material. Fractionation of extracts & isolation of Calanolides. Repatriation of data, training of Sarawak scientist at DTP labs & transfer of screening capabilities. Support for surveys and sustainable management of <i>C. teysmannii</i>. 	<ul style="list-style-type: none"> Investment of capital & synthetic chemistry expertise in development of Calanolides. Training of Sarawak scientist and physicians in preclinical and clinical work; provision of space, administrative services and scientific personnel to SMP. Synthesis of (+)-Calanolide A. Processing of imported <i>C. teysmannii</i> latex to produce (-)-Calanolide B. 	<ul style="list-style-type: none"> Collaborative work with the UIC for collection of specimens, species surveys & sustainable management of <i>C. teysmannii</i>. Logistical support including vehicle, & field, nursery & herbarium staff. Funding for the further development of Calanolides. Supply of <i>C. teysmannii</i> latex for production of (-)-Calanolide B. Appointment of scientists for training. 	<ul style="list-style-type: none"> Coordination for research & development into Calanolides, e.g. site selection for clinical trials of (+)-Calanolide A, allocation of incoming funding. Mechanism for sharing benefits. Work on (-)-Calanolide B and other Calanolide candidates by qualified SMP scientist trained at Medichem Research.
Monetary benefits:	<ul style="list-style-type: none"> Funding from the NCI. Share in NCI's royalties from SMP (based on co-authorship of patent). 	<ul style="list-style-type: none"> Undisclosed royalties from SMP. 	<ul style="list-style-type: none"> 50% share in undisclosed royalties arising from patents filed by SMP. 	<ul style="list-style-type: none"> Collection fees? 50% share in royalties arising from SMP patents. 	<ul style="list-style-type: none"> All benefits distributed to Medichem Research and the Sarawak Gov't.
Non-monetary benefits:	<ul style="list-style-type: none"> Access to material, information exchange. 	<ul style="list-style-type: none"> Accelerated development of Calanolides through input by Medichem Research/ SMP. The NCI was able to divert its limited resources elsewhere. Right to continue working on Calanolides as agreed to by Sarawak Gov't. 	<ul style="list-style-type: none"> Exclusive right to develop NCI-patented Calanolides, subject to royalty-sharing. Access to Sarawak Gov't. funding for clinical trials of (+)-Calanolide A & further such funding for the development of other Calanolides. 	<ul style="list-style-type: none"> Input of UIC expertise; data repatriation; conservation and sustainable use of <i>C. teysmannii</i>. Exclusive rights to supply <i>C. teysmannii</i> latex. Training of scientist in screening and isolation techniques at the NCI & in drug development at Medichem Research. Screening capabilities from the NCI. 	<ul style="list-style-type: none"> All benefits distributed to Medichem Research and the Sarawak Gov't.

BENEFITS

Benefits shared under collaborative arrangements between the UIC and the Sarawak Forestry Department

The UIC benefited from extensive logistical support from the Sarawak Government, including a vehicle and provision of field, nursery and herbarium staff. In return, the State gained from the UIC's expertise in the design, formulation and monitoring of investigations and experiments in the field,⁹⁶ a long term benefit of which has included the sustainable harvest of *C. teysmannii* latex. The UIC also undertook responsibility for the communication of any results to its Sarawak counterparts.⁹⁷ Two Sarawak scientists, Dr. Muney Serit and Dr. Haji Othman, worked with UIC staff in the field.⁹⁸

Benefits shared under the 1993 SBIR grant and the 1995 exclusive license to Medichem Research

The 1993 SBIR grant provided Medichem Research with the means to pool its own expertise in synthetic organic chemistry with the NCI's research capacity. That expertise has been essential to processes including the bulk synthesis of (+)-Calanolide A for preclinical studies. Furthermore, Medichem already held patents on other synthetic anti-virals (e.g., against hepatitis-B). Licensing the compounds to Medichem Research enabled NCI to ensure the development of Calanolides as effective anti-AIDS therapeutics. Whilst the NCI provided research facilities at their own cost and in-kind contributions of know-how, the SBIR grant enabled Medichem Research to commit investments which the NCI would not have been able to make in light of other research priorities.

With the 1995 license to develop and commercialise Calanolides came four key benefits. Firstly, the earlier a compound is licensed to a company, the sooner the NCI can divert its limited resources into other less advanced projects.⁹⁹ Secondly, the license afforded Medichem Research a high degree of exclusivity, providing a strong incentive for further investment. Thirdly, it provided the basis on which the SMP joint venture could operate. Finally, the NCI stands to gain royalties on the license, some of which are returned to NCI inventors, and Dr. Soejarto, the UIC inventor, as an incentive, but most of which are reinvested in anti-cancer and anti-HIV research.

Benefits shared under the 1994 Letter of Collection-based agreement

NCI's commitments to technology transfer and source-country capacity building under the 1994 Letter of Collection were first realised when Dr Muney Serit, a senior Sarawak scientist then working at the University of Malaysia Sarawak (UNIMAS), spent ten and a half months at the NCI's Frederick Cancer Research and Development Centre to gain exposure to the Institute's screening and isolation techniques and one and a half months at the UIC laboratories.¹⁰⁰ He then returned to Sarawak in April 1995 and initiated a project for the isolation of (-)-Calanolide B. The transfer of screening capacity, including appropriate cell lines, has still to materialise since there is a lack of suitable facilities in Sarawak. The formation of the joint venture is owed to the requirement under the Letter of Collection for NCI to ensure that Medichem Research was apprised of the terms of the Letter of Collection

⁹⁶ Personal communication, Dr. Doel Soejarto, College of Pharmacy, University of Illinois at Chicago, 9 March 1998.

⁹⁷ Personal communication, Dr. Doel Soejarto, College of Pharmacy, University of Illinois at Chicago, 9 March 1998.

⁹⁸ Personal communication, Dr David Frodin, RBG Kew, 9 March 1998 and Dr. Doel Soejarto, UIC, 19 April 1998.

⁹⁹ Personal communication, Dr Gordon Cragg, National Cancer Institute, 3 March 1998.

¹⁰⁰ Personal communication, Dr. Doel Soejarto, College of Pharmacy, University of Illinois at Chicago, 19 April 1998.

Benefits shared through the joint venture, Sarawak Medichem Pharmaceuticals Incorporated (SMP)

The State Government of Sarawak is providing funding up to an agreed point in the clinical development of (+)-Calanolide A (i.e. completion of Phase I). After this stage in the research, additional funds will be raised by the two parties, through a variety of mechanisms, to permit the drug's passage through the next, and more expensive, phases of clinical trials. SMP has a number of additional sources of funding to develop other promising Calanolides, including (-)-Calanolide B, and the National Institutes of Health (NIH) has awarded Medichem Research personnel Small Business & Innovative Research Grants (SBIR) to the same end. Currently, royalties that arise once the drug is marketed will be split 50:50, based on the contribution of chemical knowledge and expertise by Medichem Research and the contribution of investment by Sarawak. The sharing of benefits may change depending on how the current investment patterns develop over time. To date, all drug development under the venture is conducted at Medichem Research in the USA. Medichem Research also operates for SMP in the capacity of an independent contractor, processing Calanolides for preclinical and clinical studies as well as providing administrative services, space and scientific personnel.¹⁰¹

Dr Tuah Jentah, a Malaysian PhD Chemist, is treasurer of SMP and has been observing the Phase IA trials in the capacity of a source country scientist. It is hoped that the drug will reach sick patients in Phase II between May and June 1998. Two Sarawak physicians will shortly be assigned to participate in the clinical work.¹⁰² Dr Tuah Jentah is also conducting preclinical studies and scheduling toxicological work on two back-up compounds, funded partly by SMP and partly by further SBIR grants.

Possibilities for future benefit-sharing

The State Assembly of Sarawak approved the creation of a 'Sarawak Biodiversity Centre' in 1997. The Centre has now been established in Kuching as an umbrella organisation, to co-ordinate existing government and academic research efforts in the conservation, sustainable management and utilisation of Sarawak's biodiversity. The State Government of Sarawak hopes that the Biodiversity Centre will co-ordinate natural product screening in Sarawak.¹⁰³ Once the necessary infrastructure is established, the NCI is prepared to transfer to Sarawak its anti-cancer and anti-HIV cell lines, and is likely to seek a close collaboration with the Centre within the framework of a Memorandum of Understanding (MoU).¹⁰⁴

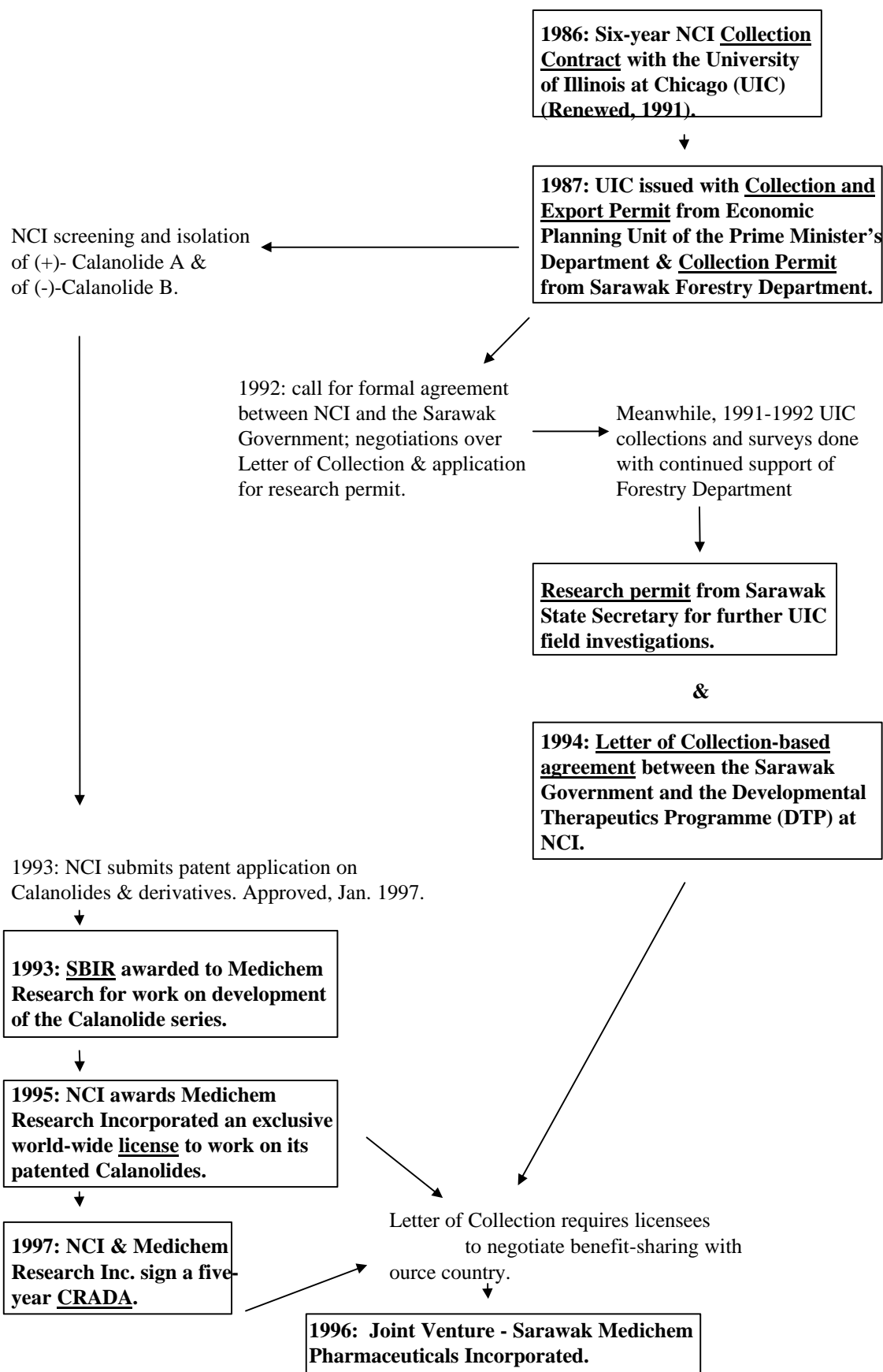
¹⁰¹ Personal communication, Dr Tuah Jenta, Sarawak Medichem, 18 February & 2 March 1998.

¹⁰² Personal communication, Dr Tuah Jenta, Sarawak Medichem, 18 February & 2 March 1998.

¹⁰³ The Biodiversity Centre also has an agreement with the Australian pharmaceutical company AMRAD, for extraction, isolation and bioassay of plant material from the Sarawak rainforest. The agreement involves provision of materials and training, as well as technology transfer. Personal communication, Dr Tuah Jenta, Sarawak Medichem, 18 February & 2 March 1998.

¹⁰⁴ Personal communication, Dr Gordon Cragg, National Cancer Institute, 9 February 1998.

PROCESS FOR ESTABLISHING THE ARRANGEMENTS.



IMPACT ON CONSERVATION

Observations at the Sampadi Forest Reserve, the Kubah and Bako National Parks (where it featured significantly in scrub succession on sandy Soils¹⁰⁵) and Sematan at Gunung Pueh demonstrate that both species of *Calophyllum* are common in Sarawak, and are not endangered.¹⁰⁶ They are recognised timber species, known generically in Malaysia and Indonesia as “Bintangor”. In 1994, Peninsular Malaysia exported 8330 cubic metres of *Calophyllum* at \$198.78 per cubic metre.¹⁰⁷ However, the Sarawak Forest Department moved to ban their felling in June 1993 in the light of the recent loss of a critical specimen of *C. Lanigerum* and the species’ potential as a source of an anti-HIV drug; a move which may help to secure their long-term survival.¹⁰⁸

Potential for the sustainable harvest of *C. lanigerum* is negligible as the critical specimen that was originally sourced was lost. In addition to differences in immediate growing environment and morphological variation between individuals,¹⁰⁹ drought and smoke haze may also have had an influence on the reduced (+)-Calanolide A content of many of the trees sampled,¹¹⁰ although genetic factors are likely to predominate.¹¹¹ This is an interesting point in light of current climatic conditions in Borneo. Synthesis of (+)-Calanolide A is therefore the only option, adding little to the existing conservation value of this species. However, experiments transplanting more than 6000 seedlings were conducted by the Sarawak Forestry Department, and demonstrated a high survival rate.¹¹²

By contrast, the conservation value of *C. teysmannii* has been significantly increased. As Dr. Soejarto discovered,¹¹³ its latex, rich in (-)-Calanolide B¹¹⁴, can be repeatedly tapped by making small slash wounds in the bark of mature trees without harming them.¹¹⁵ Inspections of trees six months after tapping revealed no adverse effects. Future experiments will assess harvest optimisation and long-term effects (5 to 10 years).¹¹⁶

Investigators believe that this method of harvesting *C. teysmannii* is both reliable and replicable. Techniques used for extracting the tree’s resinous latex have long been practised for the extraction of sap from *Pinus sylvestris*, benzoin from *Styrax benzoin*, karaya gum from *Sterculia urens* and storax from *Liquidambar orientalis* and *L. styraciflua*. Some refinements will, however, be inevitable.¹¹⁷ For example, there may be a chemical which can further stimulate latex flow from the incised bark of *C. teysmannii*, thus reducing the number of incisions required. There may also be some consideration of anti-bacterial and anti-fungal treatment of old incisions.¹¹⁸

¹⁰⁵ Personal communication, Dr David Frodin, RBG Kew, 9 March 1998.

¹⁰⁶ Personal communication, Dr Doel Soejarto, College of Pharmacy, University of Illinois at Chicago, 9 March 1998.

¹⁰⁷ Expsaw; Table 6-2-b, Major Tropical Sawnwood Species Exported by ITTO Producers, 1994.
<http://itto.or.jp/timber_situation/timber1995/tables/6-2-b.htm>.

¹⁰⁸ Personal communication, Dr Doel Soejarto, College of Pharmacy, University of Illinois at Chicago, 9 March 1998.

¹⁰⁹ Mays, T. D., K. D. Mazan, G. Cragg, M. Boyd, *A paradigm for the Equitable Sharing of Benefits Resulting from Biodiversity Research and Development*, in Grifo & Rosenthal, “Biodiversity and Human Health”, 1997 Island Press & Personal communication, Dr David Frodin, RBG Kew & Dr Doel Soejarto, College of Pharmacy, University of Illinois at Chicago, 9 March 1998.

¹¹⁰ Personal communication, Dr David Frodin, RBG Kew, 9 March 1998.

¹¹¹ Personal communication, Dr. Doel Soejarto, College of Pharmacy, University of Illinois at Chicago, 19 April 1998.

¹¹² Personal communication, Dr. Doel Soejarto, College of Pharmacy, University of Illinois at Chicago, 9 March 1998.

¹¹³ On the basis of this work, Dr. Soejarto was named co-author of an NCI patent. Personal communication, Dr. Doel Soejarto, University of Illinois at Chicago, 21 April 1998.

¹¹⁴ With over 20% content. Mays, T. D., K. D. Mazan, G. Cragg, M. Boyd, *A paradigm for the Equitable Sharing of Benefits Resulting from Biodiversity Research and Development*, in Grifo & Rosenthal, “Biodiversity and Human Health”, 1997 Island Press.

¹¹⁵ Cragg et al., *Drug discovery and development at the National Cancer Institute: potential for new pharmaceutical crops*. <<http://www.hort.purdue.edu/newcrop/proceedings1996/>>.

¹¹⁶ Personal communication, Dr. Doel Soejarto, College of Pharmacy, University of Illinois at Chicago, 9 March 1998.

¹¹⁷ In the case of *Pinus sylvestris*, spraying the incised bark with sulphuric acid stimulated resin flow. Personal communication, Dr. Doel Soejarto, College of Pharmacy, University of Illinois at Chicago, 9 March 1998.

¹¹⁸ Personal communication, Dr. Doel Soejarto, College of Pharmacy, University of Illinois at Chicago, 9 March 1998.

Potential for transplanting *C. teysmannii* seedlings was also investigated by the Forestry Department, and between 1994 and 1995, 2000 seedlings were re-planted in secondary forests. Future assessment will include the physiological and ecological effects of replanting.¹¹⁹ As regards differences in (-)-Calanolide B content between individuals of *Calophyllum teysmannii*, a study is being undertaken by Marian Kadushin from the UIC based on fieldwork conducted between 1994 and 1996. One aim of this research is to identify especially productive specimens for clonal multiplication for industrial production.

Based on these studies, the Sarawak Biodiversity Centre is reportedly to begin further investigations of the planting and nurturing of *Calophyllum teysmannii* as a sustainable source for the production of (-)-Calanolide B¹²⁰, both for current trials and, if the drug is a success, on a commercial scale.

THE CASE OF TOPOTECAN

LEGAL AND POLICY CONTEXT

SMITHKLINE BEECHAM'S CORPORATE POLICY ON ACCESS AND BENEFIT SHARING

When SB obtained access to Camptothecin from the NCI's collections, SB, like most companies at the time, had no corporate policy on access to genetic resources and benefit-sharing. Subsequently, SB has developed a corporate policy to share the benefits arising from the development of new natural product discoveries with source countries of the genetic resources on which those discoveries are based.^{121,122}

LAW AND POLICY ON ACCESS TO GENETIC RESOURCES AND BENEFIT-SHARING IN CHINA

In the early 20th Century when *Camptotheca acuminata* was initially collected, China, in common with most countries, had little regulation of access to genetic resources. China also had few opportunities to share in any benefits arising from use of its genetic resources abroad. Recent laws suggest that this is no longer the case.

At the United Nations Conference on Environment and Development, Premier Li Peng signed the CBD, and China ratified the Convention on 5 January 1993. In 1993, the National Biodiversity Unit (NBU) was established with the approval of the State Council as an inter-ministerial coordinating group for CBD implementation. The NBU is headed by the National Environmental Protection Agency (NEPA), and comprises 20 governmental bodies that report to the State Council. To date, China has developed and launched a Biodiversity Conservation Action Plan and prepared a National Report on Biodiversity.

There are currently four main laws in China that involve the regulation of access.

¹¹⁹ Personal communication, Dr. Doel Soejarto, College of Pharmacy, University of Illinois at Chicago, 9 March 1998.

¹²⁰ Personal communication, Dr Tuah Jenta, Sarawak Medichem, 18 February & 2 March 1998.

¹²¹ Although SB has discontinued its direct participation in bioprospecting and is now placing resources in combinatorial chemistry, SB's collaborators who do bioprospect must themselves negotiate appropriate agreements with source countries. If, however, plants and marine organisms are submitted for screening at SB, the company will itself take all necessary steps to share benefits. Personal communication, Dr Randall Johnson, SB, 19 March 1998.

¹²² An example of SB's practice in benefit-sharing lies in its partnership with Rhodes University, South Africa in the early 1990s under which the company undertook to pay for costs incurred by collecting, taxonomic studies and the naming of specimens. In addition, it undertook to pay a sample fee to cover laboratory expenses, participation of Rhodes collaborators at international conferences and the training of students. Source: S.A. Laird & Wynberg P.W., *Bioprospecting in South Africa*, July 1996.

The Wild Animal Protection Law (1989) provides that wild animals belong to the State,¹²³ protects the animals and their habitats, and bans certain hunting and other activities,¹²⁴ and prohibits the selling and buying of protected animals and derived products.¹²⁵ Access for scientific research, artificial breeding and other 'special uses' requires the permission of the responsible ministry of central government, or by an institution authorised by central government to exercise such authority.¹²⁶ The export of protected animals and products derived for them requires the approval of the responsible ministry or the State Council, with additional permission needed from the administrative office for the export and import of endangered species, as appropriate.¹²⁷ Field surveys and the taking of photographs or films by foreigners requires permission from the responsible ministry or its authorised institution, as do hunting activities by foreigners.¹²⁸

The Wild Plants Protection Regulation was issued by the State Council on 1 January 1997. This measure protects wild plants and their habitats, and prohibits illegal collection of wild plants and destruction of their habitats.¹²⁹ The State bans the collection of plants of the highest category of protection, and subjects access to them for scientific research, artificial breeding and other special uses to permission from the responsible ministry under the State Council, or from the institution authorised by that ministry to determine access.¹³⁰ Before an applicant for a permit applies to the responsible ministry, he or she must also obtain a signature from the responsible department of the local provincial government.¹³¹ For plants categorised as having the 'second-grade' level of protection, an applicant should obtain a permit from the appropriate provincial institution, having first obtained permission from the authorities in the county local to the proposed collecting activities.¹³² Sale and purchase of 'first-grade' protected plants is prohibited, while sale and purchase of 'second-grade' protected plants requires the approval of the responsible department of provincial government or an institution authorised by the department to administer such permits.¹³³ Applications to import and export wild plants protected by national law or international conventions are to be examined by the responsible local provincial department and then approved by the State Council. In addition, a certificate of permission is needed from the national administrative institution for endangered species.¹³⁴ The export of 'unnamed or new wild plant species with important values' is banned, and foreigners are prohibited from collecting or purchasing wild plants protected by Chinese law.¹³⁵ Field investigations in the habitat of such plants require permission from the responsible local provincial department and then approval by the responsible ministry of central government.¹³⁶

The Regulation for Seeds Management entered into force on 1 May 1991, when issued by the State Council. This measure covers reproductive materials (such as seeds, fruit, nuts, roots, stems and seedlings) for use in agriculture and forestry.¹³⁷ It provides for their conservation and utilisation by the State,¹³⁸ and the registration of seed introduced from abroad.¹³⁹ The exchange of germplasm with foreigners is subject to rules issued by the Ministry of Agriculture and the Ministry of Forestry, which date

¹²³ Article 3, Wild Animal Protection Law, 1989.

¹²⁴ Articles 8 and 16, *ibid.*

¹²⁵ Article 20, *ibid.*

¹²⁶ Article 20, *ibid.*

¹²⁷ Article 24, *ibid.*

¹²⁸ Article 26, *ibid.*

¹²⁹ Article 9, Wild Plants Protection Regulation, 1997.

¹³⁰ Article 16, *ibid.*

¹³¹ Article 16, *ibid.*

¹³² Article 18, *ibid.*

¹³³ Article 18, *ibid.*

¹³⁴ Article 20, *ibid.*

¹³⁵ Article 20, *ibid.*

¹³⁶ Article 21, *ibid.*

¹³⁷ Article 2, Regulation for Seeds Management, 1991.

¹³⁸ Article 8, *ibid.*

¹³⁹ Article 9, *ibid.*

from June 1991.¹⁴⁰ These provide that the germplasm of crops are deemed to belong to the State and are protected from damage.¹⁴¹ Their exchange for research is administered by the Institute of Crop Germplasm Resources of the Chinese Academy of Agricultural Sciences.¹⁴² The importation of crop germplasm is encouraged,¹⁴³ but any organisation and individual providing crop germplasm to foreign countries is required to abide by certain formalities established in rules that vary according to the nature of the germplasm.¹⁴⁴ Similar provisions exist with respect to tree seeds.¹⁴⁵

The fourth piece of legislation concerning access to genetic resources in China is the Regulation of Breeding Stock and Poultry Management of 1 July 1994. Covering domestic animals and poultry and their 'genetic materials',¹⁴⁶ this measure protects the genetic resources of these animals and provides for the establishment of protected areas, farms and genebanks to conserve them.¹⁴⁷ The introduction from abroad or export to foreign countries of these resources is subjected to certain rules.¹⁴⁸

These laws appear to contain no explicit provisions related to benefit-sharing, but the requirement to obtain permission provides the opportunity for the Chinese authorities and an applicant for access to reach 'mutually agreed terms', including upon the sharing of benefits, as foreseen in the Convention. This may help China to secure a share of benefits in the future, but is of little relevance to the subject of this case study - Topotecan - since the samples of *C. acuminata* from which the precursor compound Camptothecin was derived were obtained in the early 20th century, well before the laws described above were introduced.

LAW AND POLICY ON ACCESS TO GENETIC RESOURCES AND BENEFIT-SHARING IN INDIA

Prior to recent international developments such as the CBD, the law in India related to access to genetic resources could be found in 31 different Acts related to conservation and sustainable use, and the Convention on International Trade in Endangered Species of Fauna and Flora (CITES). Prior to 1980, it was administered by a number of different government agencies, but since 1980, the regulation of access to genetic resources has fallen under the purview of the Ministry of the Environment, Forests and Wildlife. As a response to the CBD, India is developing draft access legislation.

An Expert Committee in India constituted by the Ministry of the Environment and chaired by Dr. M.S. Swaminathan is currently developing a Biological Diversity Act, whose objectives include the regulation of access to biological resources and information related thereto; the sharing of benefits with the 'conservers of biological resources' and the 'creators and holders of knowledge and information relating to the use of biological resources'.¹⁴⁹ Other objectives of the draft Act include the designation of Biological Diversity Heritage Sites; the protection of threatened species; the involvement of local bodies in the sustainable management of biodiversity; and the preparation of biodiversity registers.

The Act will provide for the establishment of institutions at the national, State and local levels, including a National Biological Diversity Fund. This will contain appropriations made by Parliament and fees and charges levied for access, and will be used for benefit-sharing with conservers of biological resources as well as with creators and holders of knowledge and information relating to their use. Similar State

¹⁴⁰ Article 10, *ibid.*

¹⁴¹ Article 12, Detailed Enforcement Rules of the Regulation for Seeds Management on Crop Seeds, 1991.

¹⁴² Article 16, *ibid.*

¹⁴³ Article 17, *ibid.*

¹⁴⁴ Article 19, *ibid.*

¹⁴⁵ Detailed Enforcement Rules of the Regulation for Seeds Management on Tree Seeds, 1995.

¹⁴⁶ Article 2, Regulation of Breeding Stock and Poultry Management, 1994.

¹⁴⁷ Articles 6 and 7, *ibid.*

¹⁴⁸ Article 9, *ibid.*

¹⁴⁹ Brief Outline of the proposed Biological Diversity Act, in Report of the Expert Committee on Biodiversity Legislation constituted by the Ministry of Environment and Forests under the Chairmanship of Dr. M.S. Swaminathan.

Biological Diversity Funds will also be established.¹⁵⁰ The National Biodiversity Authority (NBA) will create a committee on access and benefit-sharing and will establish guidelines on access and benefit-sharing.¹⁵¹ State Biodiversity Boards will advise State Governments on conservation, sustainable use and benefit-sharing and on the utilisation of the State Biological Diversity Fund. They will also advise State Governments on implementation of the guidelines established by the NBA.¹⁵² The State Biodiversity Boards may assist local bodies to set up Biodiversity Management Committees at the village level, and to promote and record conservation and sustainable use practices.¹⁵³

The draft Act proposes to prohibit any person who is not a citizen of India, or a company not registered in India, or registered there but with foreign equity participation, from obtaining any biological resources for research or for commercial utilisation. The collection of samples of any activities ‘in the nature of collection or bioprospecting’ by such individuals would also be prohibited without the prior approval of the NBA.¹⁵⁴ Indian citizens or organisations would be prohibited from transferring the results of research in exchange for payment to any foreign person or organisation without the previous approval of the NBA, although publication of research papers or dissemination of knowledge in workshops would not be deemed a ‘transfer’.¹⁵⁵ To complement this prohibition, however, a provision is proposed to ‘facilitate transfer of biological resources to institutions abroad under collaborative research projects/exchange of information with Foreign Governments’, to encourage collaborative research projects and agreements between government-sponsored organisations.¹⁵⁶

A separate article in the draft, ‘Prior intimation regarding commercial application’, prohibits any individual from applying for ‘any form of intellectual property protection in India or abroad based on research and information gathered from any source on a biological resource occurring in the wild, cultivated or domesticated without giving prior intimation’ to the NBA in a form to be prescribed by that body.¹⁵⁷

The provisions in the current draft on benefit-sharing are relatively brief. The NBA is authorised to pay the conservers of biological resources and the creators and holders of knowledge about such resources, in recognition of their contribution. The procedure for sharing benefits with them will be regulated under rules to be made by the NBA.¹⁵⁸

As with China, these rules are currently under consideration, but were not in place at the time samples of *N. foetida* were sourced in the late 1980s and early 1990s.

OBJECTIVES OF THE ACTORS

SB entered into the National Cooperative Drug Development Group (NCDDG) with the NCI, Johns Hopkins University (JHU) and the Universities of Florida and Virginia in order to have the opportunity to work with academic investigators with a known track-record in research, in order to take advantage of the expertise of NCI’s clinical investigators, and to obtain more exposure for Topotecan.¹⁵⁹

¹⁵⁰ Article 23, *ibid.*

¹⁵¹ Article 9, *ibid.*

¹⁵² Article 10, *ibid.*

¹⁵³ Article 16, *ibid.*

¹⁵⁴ Article 17(i), *ibid.*

¹⁵⁵ Article 17(ii), *ibid.*

¹⁵⁶ Article 17(iii), *ibid.*

¹⁵⁷ Article 19(iii), *ibid.*

¹⁵⁸ Article 18, *ibid.*

¹⁵⁹ Personal communication, Dr Randall Johnson, SB, 17 April 1998.

The NCI's objective in collaborating with the Research Triangle Institute and, under the NCDDG, with SB, JHU and the Universities of Florida and Virginia, was to facilitate the discovery, development and availability of a new, natural product-based, anti-cancer drug.

JHU and the Universities of Florida and Virginia wished to collaborate with SB under the NCDDG, in order to take advantage of the company's considerable screening capacity and other research capabilities.¹⁶⁰

CONTENT AND IMPLEMENTATION OF THE ARRANGEMENTS

INPUTS

The research & discovery process

The USDA's Plant Introduction Division first obtained *Camptotheca acuminata* from the Arnold Arboretum in 1912, from stock based on seeds procured by a private collector in 1911. Further seeds were obtained directly from a private collector in 1927. Shortly after, in 1934, A.N. Steward, of the College of Agriculture and Forestry, Nanking University, also sent seeds of *Camptotheca acuminata* to the USDA, which were germinated easily at the Glenn Dale Plant Introduction Station. A number of plants were then grown and sent to various USDA plant introduction gardens including the Chico Plant Introduction Station in California. The Chico Station provided leaves of *Camptotheca acuminata* to the Biochemistry Division of the USDA's Eastern Utilisation and Development Division (EURDD) research labs in Philadelphia,¹⁶¹ one of whose objectives was to screen for plant steroidal sapogenins suitable for the synthesis of Cortisone. In total, the extracts of 7000 plants, mostly collected by botanists at the USDA's Plant Introduction Group in Beltsville, Maryland,¹⁶² were subjected to steroidal screening, as well as testing for antibiotic, antitumour and antiviral activity. In 1957, Dr Munroe Wall at EURRD was approached by the late Dr Jonathan Hartwell of the NCI. The USDA agreed to send Dr Hartwell a thousand plant extracts for anti-tumour testing at the NCI's Cancer Chemotherapy National Service Centre (CCNSC) in Bethesda, Maryland.¹⁶³ ¹⁶⁴ In 1958, Dr. Hartwell informed Dr Wall that, of all the extracts, only *Camptotheca acuminata* demonstrated activity in a number of assays.¹⁶⁵

In 1960, Dr. Wall established a natural products laboratory at the Research Triangle Institute in Durham, North Carolina, to isolate antitumour compounds in plants and other organisms under a contract with the NCI.¹⁶⁶ The NCI agreed to fund the work whilst the RTI promised to provide certain basic equipment.¹⁶⁷

In 1961, Dr Wall began fractionation of *Camptotheca acuminata* extracts from samples of wood and bark provided by the Chico station in California. By 1966, in collaboration with Dr. Mansukh Wani, he succeeded in isolating and characterising the structure of Camptothecin, the active compound. This

¹⁶⁰ *ibid.*

¹⁶¹ "*Camptothecin acuminata* Decaisne (Nyssaceae), Source of Camptothecin an Antileukemic Alkaloid" in Technical Bulletin No 1415, USDA, NCI and the Research Triangle Institute. Date unknown

¹⁶² Personal communication with Dr Munroe Wall, Research Triangle Institute, 8 April, 1997.

¹⁶³ The nature of the agreement between the National Cancer Institute and the United States Department for Agriculture cannot be recalled. Personal communication with Dr Munroe Wall, Research Triangle Institute, 8 April, 1997.

¹⁶⁴ CCNSC was later replaced by the Developmental Therapeutics Programme under the Division of Cancer Treatment, National Cancer Institute. Source: Cragg, G. et al.: *Drug discovery and development at the United States National Cancer Institute. International collaboration in search for new drugs from natural sources.*, 1994.

¹⁶⁵ Assays included the CA755 assay (then one of the NCI's standard *in vivo* cancer assays) and the lymphoid leukemia L-1210 tumour system. Source: Wall, M.E. and M.C. Wani, *Camptothecin and Analogues: From Discovery to Clinic* in "Camptothecins: new anticancer agents" Eds.: Potmesil, M. and H. Pinedo.

¹⁶⁶ Personal communication with Dr Munroe Wall, Research Triangle Institute, 8 April, 1998.

¹⁶⁷ *Ibid.*

compound subsequently proved effective against a number of tumours.¹⁶⁸ No patent was placed on Camptothecin by the RTI or the NCI.¹⁶⁹

Following Dr. Wall's work, researchers at the NCI revealed that Camptothecin could inhibit DNA and RNA synthesis.¹⁷⁰ This was of great interest to researchers seeking mechanisms by which to curb the proliferation of tumorous cells. However, it became obvious to the NCI that Camptothecin isolated from the plant was highly insoluble. This precluded its use as a drug that could be assimilated by the human body, so the NCI resorted to preparing a soluble sodium salt of the compound for administration in clinical trials.¹⁷¹ The results of the Phase I and II trials were published in 1970-1972. The salt proved to be less active than Camptothecin itself, with anti-tumour activity being observed only in some patients with gastrointestinal and bone marrow cancers. Furthermore, toxicities were so severe that trials were terminated in 1972. The NCI conducted no further work on Camptothecin for nearly twenty years,¹⁷² although research on the compound continued at the RTI¹⁷³ and in India.¹⁷⁴

Throughout the 1966 - 1972 period, additional Camptothecin was urgently required, as access to trees in the interior of China was difficult for collectors at the time. Based on Steward's stock, 1,300 seedlings were planted at the Chico station in 1966, followed by a further 5,000 in 1967 to guarantee future harvests. Meanwhile, a survey of all surviving trees on the west coast of the USA was conducted in an attempt to track down survivors of other introductions from China.¹⁷⁵ In addition, four plants were obtained from the Botanic Garden of the Taiwan Forest Institute, originally sourced from the National University, Hengchow, China.

In the mid-1980s, the NCI set up a National Co-operative Drug Development Group (NCDDG),¹⁷⁶ which provided the framework for cooperative research by SmithKline Beecham (SB), Johns Hopkins University (JHU), the University of Florida and the University of Virginia. The Group was set up to identify novel inhibitors of the enzyme Topoisomerase II. The Topoisomerases are critical to cell replication and are hence of great interest to cancer researchers.¹⁷⁷

The NCDDG's academic partners, with the appropriate assays, were primarily responsible for characterising relevant compounds, though each had their own specific targets. For example, the University of Florida undertook to conduct secondary assays of any novel inhibitors discovered by SB. SB, for its part, possessed the necessary capacity to undertake mechanism-based. The NCI was an active partner in the NCDDG, providing reagents, additional screening information¹⁷⁸ and core funding.¹⁷⁹

¹⁶⁸ Wall, M.E., and M.C. Wani: *Camptothecin and Analogues: From discovery to clinic*, in "Camptothecins: new anticancer agents" Eds.: Potmesil, M. and H. Pinedo.

¹⁶⁹ Personal communication with Dr Munroe Wall, Research Triangle Institute, 8 April, 1998.

¹⁷⁰ Work done by NCI's Dr. Susan Horowitz, David Kessel and others. Source: Wall, M.E., and M.C. Wani: *Camptothecin and Analogues: From discovery to clinic* in "Camptothecins: new anticancer agents" Eds.: Potmesil, M. and H. Pinedo.

¹⁷¹ Wall, M.E. and M.C. Wani: *Camptothecin and Analogues: From discovery to clinic* in "Camptothecins: new anticancer agents" Eds.: Potmesil, M. and H. Pinedo.

¹⁷² Introduction to *Camptothecins: new anticancer agents*. Eds.: Potmesil, M. and H. Pinedo.

¹⁷³ To date, RTI has not only found a means of synthesising 10-Hydroxy camptothecin, but has also licensed 15 patents on Camptothecin analogues to the pharmaceutical company Bristol Myers Squibb, for further development and commercialisation. Personal communication with Dr Munroe Wall, Research Triangle Institute, 8 April, 1998.

¹⁷⁴ In 1970, Professor T. R. Govindachari published an article in the Indian Journal of Chemistry, claiming to have found that *Nothapodytes foetida* also contained Camptothecin. No patent was filed on his work. Personal communication, Dr A. Venkatesvarlu, Dr Reddy's Research Foundation, Hyderabad, India, March 1998.

¹⁷⁵ Samples were taken from Los Angeles State and County Arboretum, the University of California, Huntington Botanic Garden, Oakland Park Department, and private and city gardens.¹⁷⁵ Source: "*Camptothecin acuminata* Decaisne (Nyssaceae), Source of Camptothecin an Antileukemic Alkaloid" in *Technical Bulletin No 1415. USDA, NCI and the Research Triangle Institute*.

¹⁷⁶ For further information on NCDDGs, see the Annexe to this paper.

¹⁷⁷ Topoisomerases bind double-helix DNA and interconvert its various topological forms. See Carte, B.K., and R. K. Johnson, 1996. *Topotecan Development: an example of natural product drug discovery research* in "Medicinal Resources of the Tropical Forest" Eds.: Balick, Elisabetsky and Laird.

¹⁷⁸ Personal communication, Dr Randall Johnson, Smithkline Beecham, 17 April 1998.

¹⁷⁹ See Annexe.

SB's Dr. Randall Johnson had originally worked for the NCI in the early 1970s and had a long-standing interest in Camptothecin.¹⁸⁰ Curious about its reported anti-tumour activity, including its inhibition of DNA and RNA synthesis (to which Topoisomerase enzymes are critical), Dr Johnson had obtained a sample of Camptothecin from NCI. The compound was freely available to researchers as no commercial organisation had expressed any continuing interest in it.¹⁸¹ Around the time that the NCDDG was set up, SB submitted Camptothecin to mechanism-based screening. This revealed it to be an inhibitor of the Topoisomerase I enzyme, which meant that it would be relatively tumour-specific in its activity.¹⁸² While the NCDDG's continued to focus on Topoisomerase II, JHU assisted SB in the characterisation of Camptothecin's mechanism of action, thereby providing sufficient scientific evidence to justify the compound's further development as a drug by SB.¹⁸³ JHU and SB collaborators went on to produce a joint paper explaining Camptothecin's ability to inhibit Topoisomerase I,¹⁸⁴ which greatly revived interest in the compound.¹⁸⁵

In light of these developments, SB began investigating Camptothecin derivatives designed to have lower toxicity, greater solubility and better selectivity than Camptothecin itself.¹⁸⁶ In 1986, Dr. Randall Johnson succeeded in developing Topotecan, as well as some two hundred other analogues.¹⁸⁷ Topotecan proved more active than its parent compound.¹⁸⁸ As the work that led to its development was conducted independently of the work undertaken by the NCDDG, the company subsequently filed an exclusive patent on Topotecan.^{189, 190}

Trials and production (1990 onwards)

Preclinical trials of Topotecan demonstrated an increase in the life of mice with leukemia and a high degree of activity against a wide range of human and mouse tumour models, including colon carcinomas, melanomas and lung carcinomas.¹⁹¹ Under the NCDDG, the NCI had agreed to undertake trials of any of its partners' innovations using its own funds. SB felt that the NCI's network of clinical collaborators (as coordinated by the NCI Liaison Office) would provide useful exposure for Topotecan. The company therefore undertook to supply, on a cost basis, sufficient Topotecan for the NCI to put the compound through clinical trials. At the same time, SB conducted its own parallel trials as the basis for filing an application for FDA approval of Topotecan upon completion of Phase III clinical trials.^{192,193}

¹⁸⁰ Personal communication, Dr Randall Johnson, Smithkline Beecham, 17 April 1998.

¹⁸¹ Ibid.

¹⁸² Two factors explain these discoveries. Firstly, the presence of Topoisomerase I is greatest at the 'S' phase in a cell's cycle when DNA is undergoing replication just prior to the cell splitting. If this enzyme is inhibited, that replication is stalled and the cell dies. Given that rapidly-replicating tumours are rich in 'S' phase cells, topoisomerase I is present at high levels in such tumours (including advanced human colon adenocarcinoma) but not in normal tissue. This implies that a topoisomerase I inhibitor such as Camptothecin is likely to have the greatest effect in the tumour itself. Second, the relatively higher metabolic rate of a tumour may assist in drawing in more enzyme inhibitor than other tissue.

See: (i) Hochster, H. S.: *Topotecan Clinical Trials in the United States* in "Camptothecins: new anticancer agents" Eds. Potmesil, M. and H. Pinedo. (ii) Carte, B. K., and R. K. Johnson: *Topotecan Development: an example of the evolution of natural product drug discovery research* in "Medicinal Resources of the Tropical Forest" Eds. Balick, Elisabethsky and Laird. 1996.

¹⁸³ Personal communication, Dr Randall Johnson, Smithkline Beecham, 17 April 1998.

¹⁸⁴ Shiang, Y., R.P. Hertzberg, S. Hecht and L.F. Liu, *Camptothecin induces protein-linked DNA breaks via mammalian DNA Topoisomerase I*, *Journal of Biological Chemistry*, 260 14873-88, 1985.

¹⁸⁵ Personal communication with Dr Munroe Wall, Research Triangle Institute, 8 April, 1997.

¹⁸⁶ Introduction to *Camptothecins: new anticancer agents*. Eds. Potmesil, M. and H. Pinedo.

¹⁸⁷ Personal communication, Dr Randall Johnson, Smithkline Beecham, 17 April 1998.

¹⁸⁸ Hochster, H. S.; *Topotecan Clinical Trials in the United States* in "Camptothecins: new anticancer agents" Eds. Potmesil, M. and H. Pinedo. Date not known.

¹⁸⁹ Normally, each party to a joint innovation developed under an NCDDG holds a joint patent right in that innovation and, therefore, a right to a share in downstream royalties. Personal communication, Dr Randall Johnson, Smithkline Beecham, 17 April 1998.

¹⁹⁰ Another Camptothecin derivative, CPT-11-Irinotecan was patented and developed in parallel by the Japanese company Yakult Honsha Co. Ltd.. Source: personal communication, Dr Gordon Cragg, National Cancer Institute, 9th February, 1998.

¹⁹¹ Hochster, H. S.; *Topotecan Clinical Trials in the United States* in "Camptothecins: new anticancer agents" Eds. Potmesil, M. and H. Pinedo.

¹⁹² Personal communication, Dr Randall Johnson, Smithkline Beecham, 19 March 1998.

¹⁹³ Myelosuppression was the major toxicity reported. Source: Hochster, H. S.; *Topotecan Clinical Trials in the United States* in "Camptothecins: new anticancer agents" Eds.: Potmesil, M. and H. Pinedo.

Phase I clinical trials of Topotecan were initiated in 1990 by SB and the NCI, in collaboration with a range of US and European institutions.¹⁹⁴ Following Phases II¹⁹⁵ and III¹⁹⁶, the FDA approved SB's Topotecan application in 1996 and the company is now marketing it as Hycamtin-R®.

Clinical trials and production of Hycamtin-R® on a commercial scale require large volumes of source material from a steady and dependable source. SB's chemists first produced Topotecan by semisynthesis from Camptothecin sourced from plants. Despite SB's subsequent discovery of a means for total synthesis, semisynthesis has proved more cost effective, given the low dose levels of Topotecan needed.^{197,198} Between the mid-1980s and the early 1990s, SB acquired its Camptothecin from Chinese pharmaceutical companies processing *Camptotheca acuminata* and Indian pharmaceutical companies processing *Nothapodytes foetida*.^{199,200} However, despite these options for sourcing the compound, in

¹⁹⁴ Various institutions in the U.S. performed trial infusions under the programme, including the Memorial Sloan Kettering Cancer Center, the University of Texas at San Antonio, New York University Medical Centre, the Case Western Reserve University, the MD Anderson Cancer Center, the John Hopkins Oncology Centre, Mayo Clinics, and the Fox Chase group. Topotecan pharmacokinetic studies were undertaken by the John Hopkins Oncology Center, the University of Texas at Antonio, the Fox Chase Center, the NCI and NYU Medical Centre. Phase I trials in Europe were facilitated by the NCI Liaison Office under an exchange programme with the European Organisation for the Research and Treatment of Cancer (EORTC), responsible for co-ordinating trials across Europe. Trials were conducted in the Netherlands by the drugs development unit at the Free University of Amsterdam. Source: Hochster, H. S.; *Topotecan Clinical Trials in the United States* in "Camptothecins: new anticancer agents" Eds. Potmesil, M. and H. Pinedo.

¹⁹⁵ Phase II trials took place using protocols set out by the NCI's Cancer Therapy Evaluation Programme (CTEP) [Participants included the University of Rochester *, the Southwest Oncology Group, the University of Alabama, the Dana Faber Cancer institute, Ohio State University, the National Cancer Institute of Canada, MD Anderson*, the John Hopkins Oncology Centre*, the University of Texas and NYU Medical Centre all took part. Those trials undertaken by asterisked institutions were sponsored by SB. Topotecan combination trials were undertaken by the Cancer and Leukemia Group B, the University of Texas, the John Hopkins Oncology Centre and the Gynecologic Oncology Group. The NCI Cancer Study Group conducted paediatric Topotecan trials]. Source: Hochster, H. S.; *Topotecan Clinical Trials in the United States* in "Camptothecins: new anticancer agents" Eds. Potmesil, M. and H. Pinedo.

¹⁹⁶ Phase III trials revealed Topotecan to be a second line therapy against ovarian cancer as well as being effective against small-cell lung cancers.

¹⁹⁷ Personal communication, Dr Randall Johnson, Smithkline Beecham, 19 March 1998.

¹⁹⁸ This is also despite the fact that RTI has developed a means of totally synthesising 10-hydroxy camptothecin, a key intermediary compound in the synthesis of Topotecan. Personal communication with Dr Munroe Wall, Research Triangle Institute, 8 April, 1997.

¹⁹⁹ Personal communication, Dr Randall Johnson, Smithkline Beecham, 19 March 1998.

around 1993, SB's Technical Division subsequently decided to obtain Camptothecin from a pharmaceutical company that acts as a broker for plant material from around the world.²⁰¹ Most of its Camptothecin supplies come from plantations of *Camptotheca acuminata* in Brazil.²⁰²

²⁰⁰ For example, further to Professor Govindachari's un-patented work in 1970, the Indian firm Attul Products supplied Smithkline Beecham until July 1993, using a process for the extraction of Camptothecin from *Nothapodytes foetida*. Personal communication, Dr A. Venkatesvarlu, Dr Reddy's Research Foundation, Hyderabad, India, March 1998.

²⁰¹ Personal communication, Dr Randall Johnson, Smithkline Beecham, 17 April 1998.

²⁰² Yakult Honsha, a Japanese company manufacturing another Camptothecin derivative, reportedly relies on plantations in Okinawa, Japan, as its principal source of Camptothecin. Personal communication, Dr Randall Johnson, SB, 19 March 1998 .

SUMMARY OF INPUTS & BENEFITS RELATED TO THE DISCOVERY AND DEVELOPMENT OF TOPOTECAN

	USDA	Research Triangle Institute.	NCI	Johns Hopkins University and the Universities of Florida and Virginia	Smith Kline Beecham	Suppliers of Camptothecin.
INPUT	<ul style="list-style-type: none"> Acquisition of <i>C. acuminata</i> from China. Cultivation of <i>C. acuminata</i>. Supply of <i>C. acuminata</i> to NCI and the Research Triangle Institute. 	<ul style="list-style-type: none"> Fractionation of <i>C. acuminata</i> extract, and isolation and structural elucidation of Camptothecin. 	<ul style="list-style-type: none"> Funding for the Research Triangle Institute's isolation of Camptothecin. Determination of Camptothecin's ability to inhibit DNA and RNA synthesis. Sponsorship of clinical trials of Camptothecin in early 1970s. Sponsorship of NCDDG. Sponsorship and conduct of clinical trials of Topotecan in collaboration with SB and coordinated clinical trials in the USA & Europe. 	<ul style="list-style-type: none"> Characterisation of compounds capable of inhibiting Topoisomerase. 	<ul style="list-style-type: none"> Discovery of Camptothecin's Topoisomerase enzyme inhibition in collaboration with Johns Hopkins University. Development of and patent on Topotecan. Clinical trials of Topotecan in collaboration with the NCI. Marketing of Hycamtin-R® (Topotecan). 	<ul style="list-style-type: none"> Discovery of Camptothecin in <i>N. foetida</i> in India. Supply of Camptothecin to SB by Chinese and Indian pharmaceutical organisations. Current supply to SB of Camptothecin by multinational broker, sourced from Brazilian plantations.
MONETARY BENEFITS	<ul style="list-style-type: none"> Unknown 	<ul style="list-style-type: none"> Sponsorship from the NCI for work on Camptothecin 	<ul style="list-style-type: none"> Unknown - no share in monetary benefits from sales of Topotecan by SB. 	<ul style="list-style-type: none"> NCDDG core funding. 	<ul style="list-style-type: none"> Profits on sales of Hycamtin-R®. 	<ul style="list-style-type: none"> Payments for supply of Camptothecin to the NCI and later SB.
NON-MONETARY BENEFITS	<ul style="list-style-type: none"> Unknown 	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> Collaboration with other actors in this case study supported the NCI's mission to promote the development of new anti-cancer agent. Rights to conduct clinical trials on Topotecan and information exchange with partners in clinical trials. 	<ul style="list-style-type: none"> Co-authorship by JHU and SB of paper on Camptothecin's ability to inhibit the Topoisomerase I enzyme & other benefits of collaborative research with an industrial partner. 	<ul style="list-style-type: none"> Collaboration with other NCDDG partners contributed to the discovery of Camptothecin's Topoisomerase enzyme inhibition. Co-authorship with SB of paper on Camptothecin's ability to inhibit Topoisomerase enzyme. NCI data from clinical trials supported IND application by SB. Patent on Topotecan. 	<ul style="list-style-type: none"> Unknown.

BENEFITS

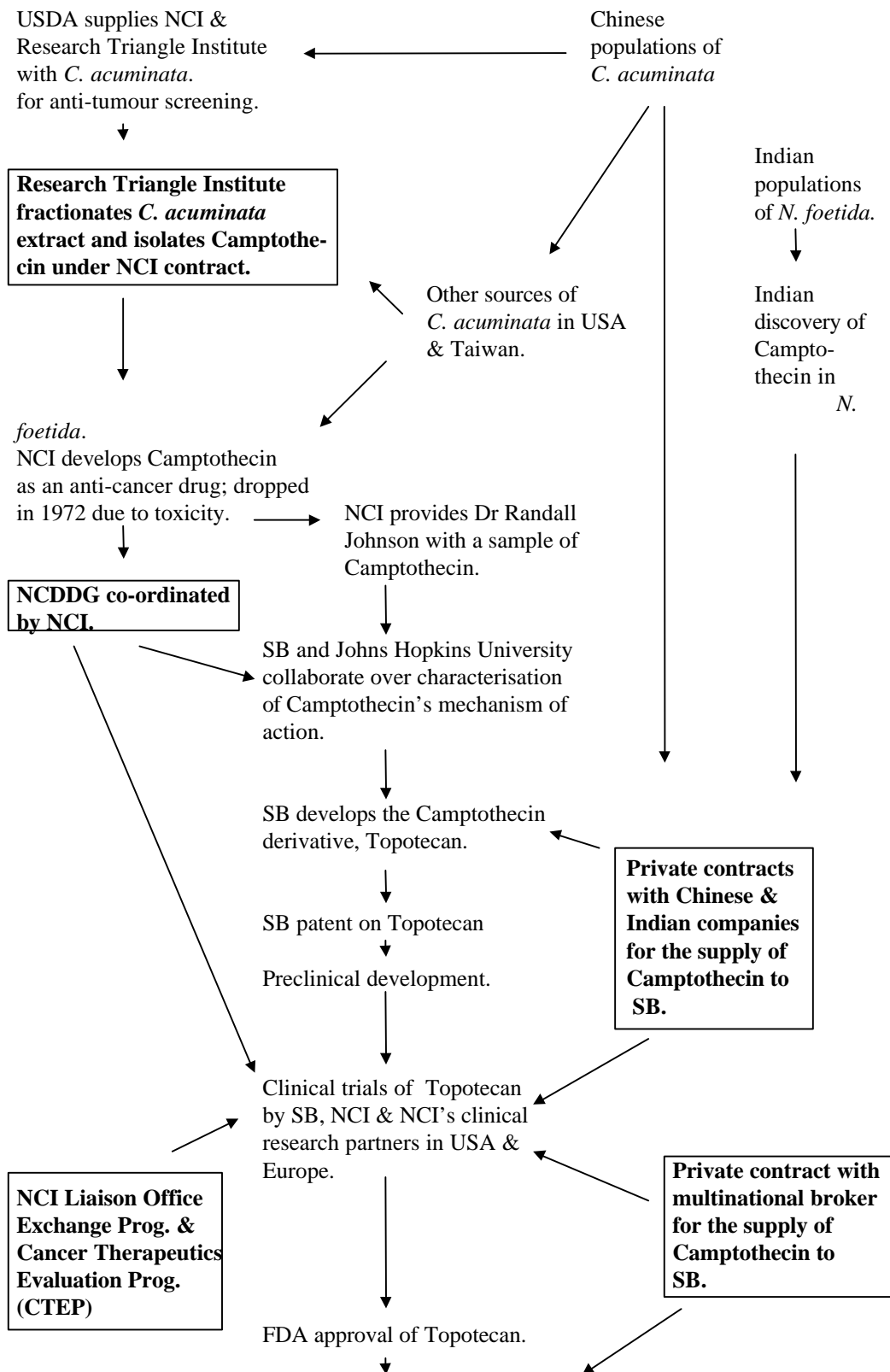
In the course of the different research partnerships that led to the development of Camptothecin and later of Topotecan, the various collaborating institutions received benefits including the provision of research funding, access to expertise within academia and access to supplies of *C. acuminata* for the research. From this distance of time it is impossible to say exactly what benefits were enjoyed by whom. However, it is clear that the collaboration indirectly stimulated the development of Topotecan by SB, giving rise to profits for the company, while the NCI succeeded in its mission by promoting research that led to a new anti-cancer drug.

Throughout the partnerships discussed in this case study, access has remained divorced from benefit-sharing since the original supplies of plant material were not obtained under access and benefit-sharing agreements. Most of the benefits were shared between researchers in the U.S.A.. However, Topotecan happens to be a drug for which the supply of plant material for manufacture is still important. While the monetary benefits received by the current suppliers to SB are not known, at the time that the NCI and SB needed supplies for research in the early 1990s, pharmaceutical organisations in India quoted to the NCI prices ranging from US\$20,000 to US\$38,000 per kilo of Camptothecin²⁰³. Extraction technology improved around the same time and prices soon rose to US\$85,000 per kilo.²⁰⁴

²⁰³ At 92% purity. Personal communication, Dr Gordon Cragg, National Cancer Institute, 9 February 1998.

²⁰⁴ At 98% purity. Source: personal communication, Dr Gordon Cragg, National Cancer Institute, 9 February 1998.

PROCESS FOR ESTABLISHING THE ARRANGEMENTS



SB markets Topotecan as Hycamtin-R®

IMPACT ON CONSERVATION

Camptotheca acuminata

Much of *C. acuminata*'s forest habitat is now cultivated and remains only on high ground, above evergreen broadleaf forest and below montane coniferous forest. However, as the tree is used extensively as an ornamental, it is not rare. It is found along waysides and irrigation ditches in many southern provinces of China and is frequently planted around farmhouses as a source of firewood.²⁰⁵ A label on a herbarium specimen collected in 1921 noted it as a 'drug plant' and there is some demand in China for the plant for the small-scale manufacture of the Chinese anti-cancer drug *Xishu* (a microparticulate suspension of *C. acuminata*).²⁰⁶

Despite SB's current contract with a supplier sourcing from Brazilian plantations, it appears that pharmaceutical suppliers in China continue to produce Camptothecin, and demand within China for the production of *Xishu* for domestic consumption, as well as of Camptothecin for export, has led to concern about the conservation status of *C. acuminata* trees in the wild.²⁰⁷ If sourcing of *C. acuminata* from the wild is not regulated, individual specimens with especially high Camptothecin content might be lost. The identification of high-yielding trees is of particular importance to propagation and sustainable harvesting (including coppicing) but there is still insufficient understanding of the factors that may cause the Camptothecin content to vary.²⁰⁸ Although this may not be of immediate concern to SB's production of Topotecan, given that its potency is such that it requires only small amounts of Camptothecin as a starter, it may be pertinent for the production of other drugs such as Irinotecan and *Xishu*, which may require much greater quantities of Camptothecin. However, recent developments in China suggest that the problem of sourcing of Camptothecin may be solved by using fermentation techniques, though details are confidential.²⁰⁹ Also, the tree is well-represented *ex situ* in botanic gardens and in plantations. Cultivation is taking place on a significant scale in eastern Texas and Louisiana in the U.S.A.,^{210,211} as well as in Brazil.

Nothapodytes foetida

N. foetida is a far richer source of Camptothecin than *C. acuminata*.²¹² Wild populations in the warm, broad-leaved forests of the Himalayan foothills in northern India,²¹³ support the sourcing of this plant for pharmaceutical production.²¹⁴ There appears to be considerable variability in Camptothecin content depending on location and other environmental factors,²¹⁵ and deforestation represents a threat to the plant, for which there is still some demand. For example, Dr. Reddy's Research Foundation in Hyderabad is interested in Camptothecin for its own drug development programmes and has its own process for

²⁰⁵ "*Camptothecin acuminata* Decaisne (Nyssaceae), Source of Camptothecin an Antileukemic Alkaloid" in Technical Bulletin No 1415, USDA, NCI and the Research Triangle Institute.

²⁰⁶ Personal communication, Professor Chen Jin, Xishuangbanna Botanical Garden, Yunnan, 6 March, 1998.

²⁰⁷ Ibid.

²⁰⁸ Ibid.

²⁰⁹ Ibid.

²¹⁰ Personal communication, Dr Randall Johnson, Smithkline Beecham, 19 March 1998.

²¹¹ Linked to the east Texas initiative is a publication on the Chinese *C. acuminata*-based medicine "Xishu" See: Shiyouli & Adair, K. T.: *Xishu*, MRM Rockwell, 1994. Personal communication, Dr Munroe Wall, Research Triangle Institute, 8 April, 1998. It is not clear if the supplies of Camptothecin from the USA have yet found a market.

²¹² Personal communication, Dr A. Venkatesvarlu, Dr Reddy's Research Foundation, Hyderabad, India, March 1998.

²¹³ Grierson A. J. C. & Long D. G. *Flora of Bhutan* Volume 2 part 1. Royal Botanic Gardens, Edinburgh, 1991.

²¹⁴ Personal communication, Dr A. Venkatesvarlu, Dr Reddy's Research Foundation, Hyderabad, India, March 1998.

²¹⁵ Ibid.

isolating the compound from *N. foetida*.²¹⁶ As regards export, it is unclear if India is still servicing an overseas market. Dr Reddy's does not itself export²¹⁷ and Atul Ltd. in Gujarat, which supplied the NCI and SB in the past, has now ceased production.²¹⁸ The conservation status of *N. foetida* is nevertheless still a matter of concern and the Indian government has moved to ban export of the whole plant.²¹⁹ Access to the plant in the wild now requires permits from the forestry authorities.²²⁰

CONCLUSIONS

LEGAL AND POLICY FRAMEWORK²²¹

CONSTRAINTS UPON THE NCI'S POWERS TO ENTER INTO BENEFIT-SHARING ARRANGEMENTS

The ability of an institution involved in access agreements to enter into legally binding benefit-sharing commitments is strongly influenced by the legal and policy framework prevailing in the country where the institution is based. Public institutions, in particular, are frequently limited by their own mandates and by public law to a few, specific mechanisms through which they can share benefits.

As an agency of the U.S. Federal government, the role of the NCI in drug discovery and development and in partnerships with private sector parties is tightly prescribed by specific statutory authority. Without such authority, the NCI is generally not able to act, so that the statutory authority that exists defines the ability of the NCI to enter into benefit-sharing commitments. For example, the NCI is a non-profit organisation, and cannot commercialise products itself nor compete with the private sector. It may, however, patent and license its technologies and inventions on certain strict terms, enabling them to be commercialised by third parties in the private sector. The statutory authority that enables U.S. Federal agencies to license their technology and to enter into Co-operative Research and Development Agreements with companies does not permit the NCI to share royalties with countries that are the source of genetic resources, unless organisations in those source countries are involved with the NCI in innovation and are co-inventors of a patent. The NCI cannot commit itself to sharing royalties with a source country if the country concerned has granted access to its genetic resources, but is not a co-inventor of a patent. The test for inventorship under U.S. law, and its determination by the courts, is itself extremely strict.²²² In effect, the policy framework restricts the NCI to licensing technology as opposed to making payments or sharing monetary benefits, except in a few specific cases.

Similarly, where the NCI uses U.S. Federal funds to pay universities and other organisations to conduct research under contract, the organisations with whom the NCI has entered into the contracts are entitled to retain title to any patents and other intellectual property.

Finally, when the NCI grants a license, the licensee may need to be selected on the basis of open competition. In the case of either a license or a CRADA, the NCI is obliged to give 'preference' to certain

²¹⁶ However, the company does not rely on a steady supplier of the plant within India. Personal communication, Dr A. Venkatesvarlu, Dr Reddy's Research Foundation, Hyderabad, India, March 1998.

²¹⁷ Ibid.

²¹⁸ Personal communication, Dr J. M. Turel, Atul Ltd., Gujarat, India, 7 April 1998.

²¹⁹ Personal communication, Dr A. Venkatesvarlu, Dr Reddy's Research Foundation, Hyderabad, India, March 1998.

²²⁰ Ibid.

²²¹ Citations for the legal provisions concerned, and a more detailed explanation of their effect is provided in the section on the legal context for access to genetic resources by the NCI and its practice in benefit-sharing, above.

²²² Personal communication, Mr. Tom Mays, Morrison & Foerster, 17 April 1998.

categories of organisation, namely U.S. based industry, or companies whose products are substantially manufactured in the U.S., and to small businesses. Depending on the nature of the license, For a source country organisation to be selected, it would need to be better qualified than any other organisations meeting these criteria. The policy framework favours U.S. institutions, and constrains the NCI in its ability to enter into direct benefit-sharing arrangements with source country organisations.

In all these circumstances, the NCI is best able to share benefits by requiring companies and universities to which it licenses patents and technology or provides genetic resources for research to negotiate benefit-sharing directly with source countries.

The NCI has made a transition from the Letter of Intent approach, in which the NCI negotiated, on behalf of source countries, such limited benefit-sharing commitments as the policy framework allowed, to the Letter of Collection approach, in which the NCI requires its licensees to negotiate benefit-sharing directly with the source country (with NCI's assistance, as appropriate). This transition demonstrates that once institutions are familiar with the full implications of the policy framework for their partnerships, they can often design mechanisms for sharing benefits that overcome policy constraints.

Furthermore, any regulatory framework will both empower and constrain activities. It is up to the institutions entering into partnerships within the prevailing policy framework to make the most of the opportunities that it presents. For example, while the statutory authority under which NCI operates may, in some respects, limit the manner in which it can share benefits, the various mechanisms that have been authorised by U.S. statutes, such as licenses, CRADAs and small business grants, do provide a range of opportunities for source countries and companies alike, as the Calanolide case study demonstrates. Familiarity with the variety of opportunities and the associated requirements created by the policy framework is a key requirement for any institution hoping to enter into access and benefit-sharing arrangements.

REGULATION OF ACCESS TO GENETIC RESOURCES

This case study reveals another interesting feature of the policy framework in some countries, namely the division of authority to regulate access between State and Federal government. While this has not yet become an issue in the U.S.A., it is a major factor under consideration as Malaysia reviews its policy framework for regulating access and benefit-sharing.

The case studies reveal the dilemma that faces governments reviewing national law relevant to access to genetic resources, namely whether to work within existing frameworks to regulate access and benefit-sharing, or whether to opt for a more all-embracing approach. Amendment of existing provisions relevant to the regulation of access offers several challenges. Taking Malaysia as a typical example, these provisions are often sectoral (for example, within laws on forests, wildlife and fisheries), and may leave unregulated access within certain geographical areas (for example, territorial waters) or access to particular categories of genetic resources (for example, microorganisms, or, prior to the 1998 Biodiversity Centre Ordinance in Sarawak, anything other than tree species). In addition, existing laws may focus more on access and research permits than on benefit-sharing. The alternative approach of adopting a single, integrated law on access and benefit-sharing may offer more political challenges. It may necessitate the amendment of existing legislation and may require considerable coordination between, on the one hand, many government departments with responsibility for different aspects of biodiversity, which is a 'cross-cutting' issue, and, on the other hand, coordination between federal, state, regional and local governments. As the Topotecan case study showed, India, for example, is currently developing a National Biodiversity Act which provides for the regulation of access at the national, state and local levels, and which will substantially replace provisions relevant to access formerly found in 31 different Acts of Parliament.

PROCESSES FOR ESTABLISHING THE ARRANGEMENTS

Developments in institutions' policies on access and benefit-sharing can be greatly influenced by requirements of potential collaborators. In the Calanolide case, the State Attorney-General for Sarawak explained to the NCI the desire of Sarawak to be involved in the negotiation of benefits with licensee companies. This contributed to the decision by the NCI to adopt the Letter of Collection model, which requires licensee companies to negotiate directly with source countries.

The negotiating skills of individual partners can also play a major role in shaping an access and benefit-sharing arrangement. Both the NCI and Medichem Research Inc. speak highly of the negotiating skills of the Sarawak team. Skills are required not only in law and the conduct of the negotiations themselves, but also in business, science and technology in order to identify benefits of enduring value to the recipients.

Companies are frequently concerned that the process of obtaining access and benefit-sharing agreements will be time-consuming and expensive, and will delay research.²²³ In the two case studies presented in this paper, only one involved a company establishing an access and benefit-sharing agreement: namely, Medichem Research and its agreements with the NCI and with the Sarawak State Government for the development of Calanolide. Medichem Research and the NCI both reported that the negotiations proceeded smoothly and rapidly, and that research continued during the negotiations. While the NCI was negotiating the Letter of Collection with the Sarawak State Government, key field work continued, facilitated by the Sarawak Forestry Department. Once NCI had granted Medichem Research the license to develop Calanolide, the negotiations between Medichem Research and the State Government of Sarawak were concluded in just six months. During this period, in which the Sarawak Medichem Pharmaceuticals joint venture was established, Medichem Research continued its research on Calanolide without interruption.

INPUTS AND BENEFITS

Benefit-sharing practice has evolved over time. As this case study illustrates, the NCI has progressed from using Letters of Intent, to using Letters of Collection, and latterly, Memoranda of Understanding, each of which offers a progressively greater opportunity for benefit-sharing within the constraints provided by the policy framework, as described above. The transition to the approach prescribed by the Memorandum of Understanding reflects the desire and growing capacity of source countries for involvement in discovery and development. In the Calanolide case study, the joint venture established between Medichem Research and the State Government of Sarawak enabled the State Government of Sarawak to nominate its own scientists to participate in the development of Calanolide. The growing use of CRADAs, which allow for a more dynamic and collaborative relationship with the private sector than the simple licensing of a compound patented by NCI,²²⁴ also offers a mechanism for joint research, which can be an important element of benefit-sharing.

The transfer of technology as a component of benefit-sharing arrangements relies on the existence within recipient institutions of adequate institutional and human capacity to receive and exploit equipment and know-how. If countries wish to maximise their opportunities for benefit-sharing, they will need to take a strategic approach and plan mechanisms to receive such benefits. In the case of the State of Sarawak, the creation of a new Biodiversity Centre should enable the skills found in local institutions such as universities to be pooled, and offers a co-ordinated interface with potential users of Sarawak's biodiversity. Such a strategic approach to building capacity should enable Sarawak to add more value to its genetic

²²³ see ten Kate, K. And Laird, S., 1997. *Placing Access and Benefit-Sharing in the Commercial Context: A Study of Private Sector Practices and Perspectives*. RBG, Kew and WRII. Unpublished.

²²⁴ Personal communication, Mr. Tom Mays, Morrison & Foerster, 17 April 1998.

resources before supplying them to companies, and is at least as important a part of planning on access and benefit-sharing as the development of access legislation.

Many new naturally-derived products are ultimately synthesised. In such cases, companies need not obtain further supplies of genetic resources for scale-up and manufacture. However, an important proportion of medicines still require access to supplies of genetic resources as the basis for their production on a large scale, either because total synthesis is technologically impossible, or because it is less cost effective than using precursor compounds extracted from genetic resources. In cases such as Topotecan and Calanolide, where companies do require ongoing access to supplies of plant material, the revenue to source countries, even for supplying large quantities of 'raw' material, can be considerable. Countries providing access to genetic resources for initial exploration can negotiate in exchange some kind of commitment to source further supplies from that country. NCI's material transfer agreement requires recipients to return to the original source country for further supplies of raw material, provided that such material is readily available at a reasonable price.²²⁵ However, companies will only make such undertakings to the extent that supplies from the country in question are reliable, of high quality, and competitively priced relative to other potential sources. In addition, most companies will always wish to maintain more than one source of material, so that production would not be endangered if a natural disaster or other problem were to affect availability of supply in one source country.

Since the probability of any compound succeeding through the risky and costly stages of product discovery and development is slim, neither the company nor source countries may ever enjoy long-term benefits. Perhaps one in ten thousand compounds succeeds as far as clinical trials, and only one in three compounds entering clinical trials results in a marketable product. Indeed, of those products that do succeed as far as the market, only one in three recoups the cost of the research and development invested in it. In these circumstances, source countries are well advised to ensure that benefit-sharing arrangements provide them with some short- and medium- term benefits, whether monetary or non-monetary. In the case of Calanolide, the joint venture with the State government of Sarawak has led to the involvement of Sarawak scientists in the medium term, in product development and in monitoring the progress of clinical trials.

Not only is the probability that an individual sample will result in a new drug on the market extremely low, but the various stages involved in the development of a new product can take several decades. Take the case of Topotecan, as set out in this case study. Seeds of *Camptotheca acuminata* were originally collected in the early 20th century. Scientists were first interested in the potential anti-cancer properties of the plant in the late 1950s. The isolation of the active compound Camptothecin in the late 1960s led to the development of a potentially useful compound in the mid-1970s. Then, as a result of problems with toxicity, research was abandoned for some 15 years. In the late 1980s, new work finally resulted in the synthesis of Topotecan, a new derivative of Camptothecin. This chequered history reaches across nearly a century, with the drug discovery and development spanning five decades. In comparison, the progress of Calanolide, from the first collection in 1987 to Phase II trials planned for 1998 - just over a decade - seems remarkably quick.

These experiences suggest a number of conclusions. First, the sharing of benefits in the short- and medium- terms are important not only because of the high likelihood that the long-term benefits of a successful commercial product may never be realised, but because any long-term benefits that do result may not arise for many decades.

A second conclusion relates to the implications of research that started several decades ago. Access laws that introduce a requirement to share benefits are a relatively recent phenomenon. Thus, most recent products, and, in all likelihood, many future products will be developed from genetic resources accessed prior to the introduction of laws requiring the sharing of benefits. A good example is to be found in the

²²⁵ See the Annexe to this paper.

case study in Topotecan in this paper. The drug Hycamtin-R® went on the market in 1996, but seed of *Camptotheca acuminata* from which the drug is derived was first sent from China to the U.S. in 1911.

A third conclusion concerns the effects of lengthy research processes on the magnitude of benefits and the link between access and benefit-sharing. Any patents taken out on compounds once they are discovered will lapse some twenty years later. When patents expire, the sales generated by companies generally fall, as they lose their temporary monopoly and other companies place similar, generic products on the market. In some access agreements, the sharing of monetary benefits is linked to the life of a patent. Even in those agreements where monetary benefits continue to be shared as long as the product makes a profit, whether or not the patent has expired, the amount of those monetary benefits is likely to drop considerably once a patent has expired. Furthermore, the information published in the patent can then be exploited without need for permission from the original patent-holder. From this time on, there need be no further link between entrepreneurs using the information in the patent and the source country from where the genetic resources originated. The link between access and benefit-sharing will be severed.

What amounts to a fair share of benefits will depend upon the relative contributions of the genetic 'raw material' and the research and development leading to the end product. In order to maintain a significant share in benefits, such as sales of a new pharmaceutical product, that may ultimately arise from access, source countries are likely to need to contribute to the research and development conducted on the genetic resources. The level of risk assumed by collaborating partners in discovery and development is another important factor that determines what constitutes a fair share in the benefits that arise from drug development. In the case of Calanolide, the State Government of Sarawak has made substantial investments towards the costs of taking Calanolide through clinical trials, and so shares in the risk that the drug candidate may not succeed to the market. Both the contribution of scientists from Sarawak in the development of the drug and the fact that the joint venture shares in the costs and risks of drug development have led to Sarawak's 50% stake in any monetary benefits that may arise.

CONSERVATION

The objective of companies is to create profitable products, and not to conserve biological diversity *per se*. However, any company whose production requires a continuous supply of genetic resources will wish to secure a long-term, reliable source of the raw material. This will often require considerable study into sustainable sourcing, as in the case of Calanolide.

Even if a product is ultimately wholly synthesised, companies often need to obtain larger quantities of plant materials during the discovery and development phase. The Calanolide case study reveals the importance of conserving not only the ecosystems where biologically active resources may be found in the future, but the very specimens from which samples that demonstrate activity were originally taken. When collectors returned to take another sample from the tree that had yielded active Calanolide, it was no longer there. It took a concerted effort to find other specimens displaying similar biological activity, although the exercise led to the discovery of another compound from a related species, that may ultimately be easier to source sustainably. The Sarawak authorities are now investigating *in situ* conservation and *ex situ* propagation of the tree, to support the requirements of the SMP joint venture for a sustainable source.

The case of Topotecan reveals that companies do not always establish direct relationships with those collecting or cultivating 'raw materials' as the basis of pharmaceutical production. Indeed, in the pharmaceutical and phytomedicine markets it is quite common for companies to obtain bulk quantities of materials from private sector brokers of materials that source them from a number of countries around the world. The company producing the final product may not even know from which countries the raw material originates. Until some kind of certification system is introduced enabling consumer companies to establish the sustainable sourcing of their raw materials, the burden of monitoring conservation efforts may rest with the governments of the countries producing the raw materials. The same may be true of

initial collection for the discovery and development stage, as this is rarely conducted by a company itself, but generally through intermediaries such as the NCI and its contract collectors.

REPLICABILITY

As this case study has documented, the NCI intends to increase the proportion of its partnerships that involve the participation of source countries in research and development. The model described in the Calanolide case could well be replicable elsewhere. Indeed, joint ventures between source country organisations and the private sector could offer a viable mechanism for benefit-sharing in several countries with the necessary financial and human resources. In the case of Sarawak Medichem Pharmaceuticals, the Sarawak State Government has made a considerable financial investment to the costly and risky Phase I clinical trials, and was able to nominate qualified scientists to participate in the work. At present, the work itself is being conducted in the United States, but, as the infrastructure in Sarawak develops, more work could be conducted there. Similar possibilities exist elsewhere in the world.

ANNEX:

AN OVERVIEW OF THE POLICY OF THE UNITED STATES NATIONAL CANCER INSTITUTE ON ACCESS AND BENEFIT SHARING

The Natural Products Branch of the Developmental Therapeutics Programme (DTP), NCI, coordinates the screening of natural product materials derived from plants, marine macro-organisms, and terrestrial and marine microorganisms. In its early years, screening of natural products was mainly concerned with testing fermentation products and, prior to 1960, only 1,500 plant extracts were screened for antitumour activity. However, an Interagency Agreement (IA) with the US Department of Agriculture (USDA) in 1960, for the collection of plants for screening, initiated a systematic search for anti-cancer agents from plant sources. Collections were initially made in the U.S. and Mexico, but these were expanded to sixty countries by USDA field collections and contract suppliers. By 1982, 114,000 extracts of 35,000 plant samples (12,000 to 13,000 species) in NCI's Natural Products Repository (NPR) had been tested against a range of tumour systems used as primary screens (principally the L1210 and P388 mouse leukaemias).

Given that few novel leads were emerging from the screens and that any that did emerge did not exhibit significant activity against human solid tumours, the collection programme with the USDA was terminated in 1982.

However, technological advances, including high throughput screening, and biochemical and biomolecular understanding of the mechanisms of action of diseases, led to the introduction of new *in vitro* human cell line screens in 1985. A new AIDS therapeutic programme was also started in 1988. These developments revitalised the NCI's work with natural products.

Plant compounds discovered by the NCI with anti-cancer and anti-AIDS properties .		
Compound	Activity	Source
• Camptothecin.	• Anti-cancer.	• <i>Nothapodytes foetida</i> (India) • <i>Camptotheca acuminata</i> (South-eastern China).
• Taxol.	• Anti-cancer.	• <i>Taxus brevifolia</i> (North-western USA).
• Michellamine B.	• Anti-AIDS.	• <i>Ancistrocladus korupensis</i> (South-western Cameroon).
• Conocurvone.	• Anti-AIDS.	• <i>Conospermum incurvum</i> (Western Australia).
• (+)-Calanolide A & (-)-Calanolide B.	• Anti-AIDS.	• <i>Callophylum lanigerum</i> & <i>C. teysmannii</i> . (Sarawak, Malaysia).

In 1986, three five-year contracts were awarded for collections of plants in tropical and subtropical regions world-wide at a total cost of \$2.7million, with Missouri Botanic Gardens (MBG) [Africa], New York Botanic Gardens (NYBG) [Central and South America] and the University of Illinois at Chicago (UIC), assisted by the Arnold Arboretum and the Bishop Museum in Honolulu [SE Asia]. The contracts with MBG, NYBG and the UIC were extended for a further 5 years in September 1991 at a total cost of \$3.8 million.²²⁶

The objectives of the NCI at the time that the UIC collected the first sample of *Calophyllum lanigerum* in 1987 remain the same today: to promote the discovery and development of new anti-cancer and anti-AIDS agents. To accomplish this goal, the NCI enters into a range of different partnerships.

NCI'S COLLABORATIVE APPROACH TO DRUG DEVELOPMENT

NCI's approach to benefit-sharing with source countries is guided by its collaborative approach to drug development. The NCI uses government funding to source, screen and isolate essential natural compounds, both through intramural research programmes and through collaborative partnerships with academia, the private sector, and other public research organisations. Development can involve preclinical and clinical studies up to the point of commercialisation, but the NCI, as a government-funded, non-profit organisation, cannot commercialise any products. Any products not selected for commercialisation by the private sector, but considered of significant therapeutic value by the NCI, would be provided to the public free of charge. The chief collaborative mechanisms for drug development are:

CO-OPERATIVE RESEARCH AND DEVELOPMENT AGREEMENTS (CRADAs)

The Federal Technology Act, 1986²²⁷ and Executive Order 12591 permit a Cooperative Research and Development Agreement (CRADA) between a Federal laboratory designated by a Federal agency of the United States government, and a private sector party. A CRADA enables the transfer of technology from a Federal laboratory to a private sector party, by means of a license. Under a CRADA, a Federal agency may receive funds from a private sector party, but may not provide funds to the private sector party.²²⁸

SMALL BUSINESS INNOVATIVE RESEARCH (SBIR) GRANTS PROGRAMME

The SBIR programme is a set-aside programme designed to support innovative research by small U.S. business concerns (500 or less employees) that have potential for commercialisation of the subject of research. Such research may include the development of promising agents, such as Calanolides. The programme is divided into two phases. Phase I covers a six-month period for feasibility studies of a proposed project. Phase II covers a two-year period for development of any project considered of sufficient promise toward clinical application and commercialisation.

A variant of the SBIR programme is the Small Business Technology Transfer (SBTTR) programme which supports collaboration between small businesses and non-profit research organisations in pursuit of the same goals as the SBIR programme.²²⁹

²²⁶ Information document on the Developmental Therapeutics Program (DTP), Division of Cancer Treatment (DCT), National Cancer Institute (NCI).

²²⁷ 35 USC 3710.

²²⁸ Personal communication, Dr Gordon Cragg, National Cancer Institute, 3 March 1998 and Mr. Tom Mays, Morrison & Foerster, 17 April 1998.

²²⁹ Personal communication, Dr Gordon Cragg, National Cancer Institute, 3 March 1998.

NATIONAL CO-OPERATIVE DRUG DISCOVERY GROUPS (NCDDGs)

NCDDGs are collaborative partnerships between academic researchers and industry, for which the NCI provides core funding and, if required, technical assistance. Within each Group, the NCI plays the role of sponsor and facilitator. NCDDGs are intended to encourage synergistic interactions between novel ideas within academia and cutting edge research within industry. Each party to a joint innovation developed under an NCDDG holds a joint patent right in that innovation and, therefore, a right to a share in downstream royalties.²³⁰

NATIONAL CO-OPERATIVE NATURAL PRODUCT DRUG DISCOVERY GROUPS (NCNPDDGs)

Similar to NCDDGs, these “innovative, multi-disciplinary approaches to the discovery of new anticancer agents from natural sources”²³¹ are five-year projects to facilitate the NCI’s scientific and programmatic involvement in collaboration between the Group’s academic, non-profit and commercial participants. In 1994, the NCI set aside US\$4 million for five to seven awards under the programme.

NCI LIAISON OFFICE EXCHANGE PROGRAMME

The Cancer Therapy Evaluation Programme (CTEP) provides investigational new drugs (INDs) to investigators in foreign countries for selected clinical trials following appropriate FDA approval. Collaborators in the International Co-operative Project Assurance (ICPA) initiative can subscribe to common research protocols, providing for fast-track approval of exchange programmes, allowing participants to freely undertake transfers of materials and researchers.

BENEFIT-SHARING MECHANISMS WITH SOURCE COUNTRIES

While the majority of countries do not have detailed legislation on access and benefit-sharing, most countries have some system of regulating access to genetic resources through the issuing of permits to collectors. The experience of the NCI’s contract collectors was that when source countries were aware of the drug discovery activities to which their samples were to be put, they were reluctant to grant the necessary collecting permits without establishing agreements to safeguard their rights in the event of commercialisation. the NCI thus developed material transfer agreements between source country Governments and the NCI’s Developmental Therapeutics Program (DTP). These agreements have evolved through three distinct phases:

- **The Letter of Intent**, developed as of 1988, first used to found a formal agreement in 1990 and revised in 1991.
- **The Letter of Collection**, which replaced the Letter of Intent in 1992.
- **The Memorandum of Understanding**, initiated in 1995 and increasingly used as the model for partnerships between the NCI and qualified organisations in source countries.

²³⁰ Personal communication, Dr Randall Johnson, Smithkline Beecham, 17 April 1998.

²³¹ NCNPDDG, NIH Guide, Vol. 23, Number 21, June 3, 1994; Request for Applications.

Each of these three kinds of agreement has involved monetary and non-monetary benefit-sharing, although, as explained below, each successive model has involved greater benefit-sharing through stronger commitments to technology transfer and a greater emphasis on collaborative research and value addition in the Source Country. The agreements contain provisions on:

- intellectual property rights (involving the payment of royalties and possibilities for joint ownership of patents);
- technology transfer, training and capacity building (involving the training of source country scientists in NCI laboratories);
- confidentiality of ethnobotanical data, including prior informed consent from traditional healers prior to publication and adequate acknowledgement of their contributions;
- joint research;
- the communication of research results to source country institutions;
- resupply (collaboration over the resupply of additional material for discovery, development and scale-up for manufacture); and
- obligations on third party licensees to share benefits with the source country.

The main benefits shared under these three agreements are compared in table A, whilst processes of negotiation are compared in table B.

THE LETTER OF INTENT

The Letter of Intent was first used in a formal agreement with Madagascar in 1990.²³² There was relatively little room in the Letter of Intent for “value-addition” in the source country. Other than royalty payments, the main benefits promised to an source country were limited to the training of a scientist at the NCI and the receipt of research results (these being channelled via the Collection Contractor who had obtained field samples). No further commitments were made to involving a source country organisation in product discovery and development.

The Letter of Intent contained provisions for the commercialisation of products based on samples supplied by source countries. It stated that all licenses on patents arising out of the collaboration must refer to the Letter of Intent agreement and that all licensees must be apprised of it. When the NCI licensed any compounds derived from materials collected to third parties for further development and commercialisation, “DTP/NCI [made] its best effort to ensure that royalties and other forms of compensation [were] provided to the host country organisation and to individuals of that country, as appropriate, in an amountnegotiated with NCI, in consultation with the host country organisation.” The ambivalence of the obligation imposed by the use of the term “best efforts”²³³ proved unsatisfactory to several source country partners which were seeking greater involvement in research. Furthermore, the NCI’s ability to enter into benefit-sharing commitments is constrained by the legal framework which provides it with the statutory authority needed to enter into partnerships of this kind.²³⁴ In response, the NCI revised the Letter of Intent was 1991. The new agreement was amended and was soon renamed the Letter of Collection.

THE LETTER OF COLLECTION

The 1991 revised Letter of Intent underwent a name change in 1992 to become the Letter of Collection. It is significantly different from the old, unrevised Letter of Intent, essentially involving a shift from what was effectively a supply agreement to a more “value-added” collaboration between the NCI and a source country organisation. This is demonstrated by a commitment in the Letter of Collection’s preamble to make

²³² Personal communication, Dr Gordon Cragg, National Cancer Institute, 9 February 1998.

²³³ Ibid.

²³⁴ For a more detailed explanation, see the ‘summary of the legal context for access to genetic resources by the NCI and its practice in benefit-sharing’, above.

TABLE A

Letter of Intent, Letter of Collection and Memorandum of Understanding: benefit-sharing provisions compared

Agreement; Benefit.	Letter of Intent	Letter of Collection	Memorandum of Understanding
Monetary benefits/ royalties	<ul style="list-style-type: none"> Depends upon negotiation of benefits between a licensee of a patented product and the NCI, the source country having been consulted by the NCI. 	<ul style="list-style-type: none"> Depends upon the negotiation of benefits between a licensee of a patented product and a source country, as required by the Letter of Collection. 	<ul style="list-style-type: none"> Depends upon the negotiation of benefits between a licensee of a patented product and a source country, as required by the Memorandum of Understanding.
Intellectual property rights	<ul style="list-style-type: none"> Joint patent protection is sought for all inventions developed collaboratively by NCI and source country organisation employees. All licences on patents arising out of the collaboration refer to the agreement and all licensees are apprised of it. 	<ul style="list-style-type: none"> As for the Letter of Intent. 	<ul style="list-style-type: none"> As for Letter of Collection & the Letter of Intent.
Joint research	<ul style="list-style-type: none"> A senior source country scientist/ technician is invited to NCI's labs for one year or gains opportunity to use technology useful in furthering work under the agreement. Further development of compounds submitted by source country scientists to NCI for screening (as separate initiatives from submissions by the collection contractor) is conducted by NCI in consultation with the relevant source country organisation. 	<ul style="list-style-type: none"> During the course of the contract, the NCI (in collaboration with the source country organisation/ government), assists the appropriate source country institute with capacity building for drug discovery and research (including screening capabilities). Once an agent has been approved by the NCI for preclinical development, the basis on which source-country scientists can participate in such development is negotiated. With regard to source country participation in the further development of specific agents, sincere efforts are made to transfer knowledge and expertise to the source country organisation. Otherwise, as for the Letter of Intent. 	<ul style="list-style-type: none"> Facilities being available, the source country organisation undertakes in-house primary anti-cancer and anti-viral screening of synthetic compounds and natural extracts, for later submission to NCI screens along with data sheets. Once NCI's advanced anti-AIDS and anti-cancer screens are completed, the source country organisation undertakes bioassay-guided fractionation to isolate pure active compounds. If fractionation facilities cannot be established at the source country organisation, suitably qualified source country scientists are sent to NCI labs for isolation studies. Otherwise, as for the Letter of Collection & the Letter of Intent.

TABLE A, CONTINUED

Benefit.	Letter of Intent	Letter of Collection	Memorandum of Understanding
Technology transfer	<ul style="list-style-type: none"> None is mentioned. 	<ul style="list-style-type: none"> With regard to source country participation in the further development of specific agents, 'sincere efforts' made to transfer technology to the source country organisation, subject to IPRs. 	<ul style="list-style-type: none"> The NCI assists in providing necessary bioassays for the source country organisation to undertake fractionation, subject to available resources.
Information: research results/repatriation	<ul style="list-style-type: none"> NCI provides the results from screens of extracts to the source country (subject to confidentiality until the DTP has a chance to file patents). 	<ul style="list-style-type: none"> As for the Letter of Intent. 	<ul style="list-style-type: none"> The NCI must repatriate the results of its advanced anti-cancer and anti-HIV screens within 90 days.
Rights to supply further material/who covers costs (licensees)	<ul style="list-style-type: none"> NCI requires licensees to seek resupply of source material from source countries. The Collection Contractor collaborates with the source country organisation over possibilities for mass propagation. 	<ul style="list-style-type: none"> As for the Letter of Intent. 	<ul style="list-style-type: none"> As for the Letter of Collection & the Letter of Intent.
Transfer to third parties/licensing	<ul style="list-style-type: none"> 3rd party recipients of material sent by the NCI must compensate the source country as appropriate. 	<ul style="list-style-type: none"> As for the letter of Intent. 	<ul style="list-style-type: none"> The NCI will not distribute material to 3rd parties without prior consent from Source Countries. If a source country organisation wishes to collaborate with such 3rd parties, the NCI will put them in touch with one another.
Publications	<ul style="list-style-type: none"> Permission of a traditional healer is sought prior to publication of any information he/ she has contributed, and he/she is acknowledged. 	<ul style="list-style-type: none"> As for the Letter of Intent. 	<ul style="list-style-type: none"> Publication of data arising out of the MoU takes place at a time agreed upon by the source country organisation and the NCI.

TABLE B

Letter of Intent, Letter of Collection and Memorandum of Understanding: processes of negotiation compared

	Letter of Intent & associated agreements	Letter of Collection & associated agreements.	Memorandum of Understanding
Agreements and Parties	(1) Collector/NCI [Collection Contract] (2) Source country/Collector [Permit] Collector carries Letter of Intent with him to explain. (3) Source country/NCI [Letter of Intent].	(1) Collector/NCI [Collection Contract] (2) Source country/Collector [Permit] Collector carries Letter of Collection with him to explain. (3) Source country/NCI [Letter of Collection].	(1) Source country/NCI [Memorandum of Understanding].
Process of reaching agreement	<ul style="list-style-type: none"> (2) and (3) negotiated at the same time by the Collector as agent for the NCI. 	<ul style="list-style-type: none"> (2) and (3) negotiated at the same time by the Collector as agent for the NCI. OR (3) negotiated separately by Source country and the NCI. 	<ul style="list-style-type: none"> The NCI and the source country negotiate directly.
Negotiation with licensees of Source Country's share in benefits.	<ul style="list-style-type: none"> The licensee of a patented product agrees what benefits to share in consultation with the NCI, the source country having been consulted by the NCI. 	<ul style="list-style-type: none"> The NCI insists that the licensee of a patented product negotiates directly with the source country over royalties and other compensation. 	<ul style="list-style-type: none"> The NCI insists that the licensee of a patented product negotiates directly with the source country over royalties and other compensation (as for Letter of Collection).

“sincere efforts” to transfer technology to the source country.²³⁵ Further to this, Article 3 discusses the transfer of screening and isolation capabilities, and Article 5 contemplates collaboration between the NCI and the source country over preclinical development of selected active agents. Article 5 also outlines the transfer of knowledge, expertise and technology.

Phrases such as “in the course of the contract period” and “during such collaboration”, reveal that the Letter of Collection is not specific as to exactly when in the discovery and development process the capacities of source countries in screening and isolation would be built, or information, know-how and technology transferred. With the exceptions of preclinical studies (though, even here, the precise nature of source country involvement is not specified) and opportunities to work in NCI labs or to use “technology useful in furthering work under [the] agreement”, it is unclear whether the benefits shared by NCI are to support immediate work on the agents selected from source country genetic resources, or whether the benefit-sharing is intended to build source country capacities in the longer term. The presumption is still that the source country has little direct participation in the discovery and development of the drug candidate in question. The Letter of Collection does not stipulate the immediate transfer of screening capabilities for source country testing of extracts obtained under the agreement and no commitment is made to the immediate provision of bioassays to facilitate source country fractionation of those compounds found to be active.

Another significant development in the Letter of Collection, compared with the Letter of Intent, is that, in ensuring licensees deliver adequate compensation to the source country, the NCI is no longer involved in negotiating the monetary terms of the license between a licensee company and the source country, but instead insists on direct negotiations between the source country and the licensee, itself dropping out of the picture. Article 8 states that *“should an agent ...be licensed to a pharmaceutical company for production and marketing, DTP/NCI will require the successful licensee to negotiate and enter into agreement(s) with the appropriate Source Country Government...agency(ies) or Source Country Organisation(s)...This agreement will address the concern on the part of the Source Country Government...or Source Country Organisation(s) that pertinent agencies, institutions and/or persons receive royalties and other forms of compensation as appropriate.”*

Finally, Article 9 shows that the scope of the genetic resources and derivatives covered under the agreement are broader than those under the Letter of Intent, covering not just actual isolates of the natural product and any inventions structurally based upon them, but also synthetic compounds for which the isolate was a developmental lead, and any associated methods and uses.

THE MEMORANDUM OF UNDERSTANDING (MoU)

As the capacities of the source country to engage in drug discovery and development increase, there is more opportunity for joint collaboration between the NCI and source country organisations. The NCI is hoping to increase the proportion of MoU-style arrangements with source countries, compared to arrangements made under the Letter of Collection.

Through greater collaboration between the NCI and the source country organisation during drug discovery and development, the MoU marks a significant shift in benefit-sharing arrangements towards more value-added source country participation in scientific research. Agreements are now based on the MoU with:

- Instituto Nacional de Biodiversidad (INBio) in Costa Rica;
- the South American Office for Anticancer Drug Development, Porto Alegre, Brazil;

²³⁵ “NCI will make sincere efforts to transfer knowledge, expertise and technology related to drug discovery and development to the [appropriate Source Country Institution (SCI)] in [Source Country] as the agent appointed by the [SCG or SO], subject to provision of mutually acceptable guarantees for the protection of intellectual property associated with any patented technology. The [SCG or SO], in turn, desires to collaborate closely with DTP/NCI in pursuit of the investigations of its plants, microbes and marine macro-organisms, subject to the conditions and stipulations of this agreement.”

- Universidad Paulista, Sao Paulo, Brazil;
- Instituto De Quimica, Universidad Nacional Autonoma de Mexico;
- Facultad De Farmacia, Universidad de Panama;
- the Research Institute of Chemistry, University of Karachi, Pakistan;
- the Kunming Institute of Botany, Yunan, China;
- the Korea Research Institute of Chemical technology, Taejeon, Republic of Korea;
- National Institute of Water and Atmospheric Research, New Zealand.
- the Division of Food Science and Technology, Council of Scientific and Industrial Research, South Africa;
- the Zimbabwe National Traditional Healers association (ZINATHA), University of Zimbabwe, Harare.
- the University of Dakar, Bangladesh.²³⁶

The MoU is negotiated directly between the NCI and a source country, reflected in the fact that the source country (rather than an NCI contractor) undertakes all collection work for local screening (rather than for export to the NCI).

The MoU provides for greater participation by source country facilities in screening and fractionation. More emphasis is paid to existing source country capabilities. Where these are lacking, the NCI offers to equip the source country organisation with cell lines and appropriate bio-assays, not only as part of a general commitment to capacity building, but for the specific purposes of furthering work on anti-cancer and anti-HIV therapeutics under the MoU involved. Thus, the source country organisation has a more immediate role to play. However, it is not clear if source country participation in preclinical development of selected agents is greater under the MoU itself than under the Letter of Collection, but where the expertise and capacity exist in the source country to perform one or more of the phases of preclinical development, further appropriate agreements for collaboration may be established. Also, although not explicitly stated in the Memorandum of Understanding, if a compound isolated by the source country organisation is of sufficient merit to advance into preclinical development, the source country organisation may elect to apply for patent protection using NCI test data. The NCI data is considered routine, so the NCI makes no claim to co-inventorship and the source country organisation has sole rights to the invention.²³⁷

Reflecting the joint responsibility of the NCI and the source country to co-ordinate drug discovery and development, the NCI will not distribute materials provided by the source country organisation to other organisations without written authorisation from the source country organisation. It also provides tighter requirements for the NCI to return *in vitro* test results to the source country organisation within 90 days, with an absolute limit of 270 days, in breach of which NCI must provide the source country with a written explanation. Finally, the MoU imposes limits on the US government's royalty-free, irrevocable, nonexclusive license to manufacture and/or use any invention claimed in a patent by a source country organisation. This license is thus restricted to work involving medical research and covers only those source country patents that rely on data generated by NCI. It does not allow for treatment of patients outside clinical trials or commercial distribution. This is sufficient to permit the NCI to continue developing a drug candidate in the long term if a private-sector licensee loses interest.²³⁸

THE BENEFIT-SHARING POLICY OF NCI's NATURAL PRODUCTS REPOSITORY (NPR)

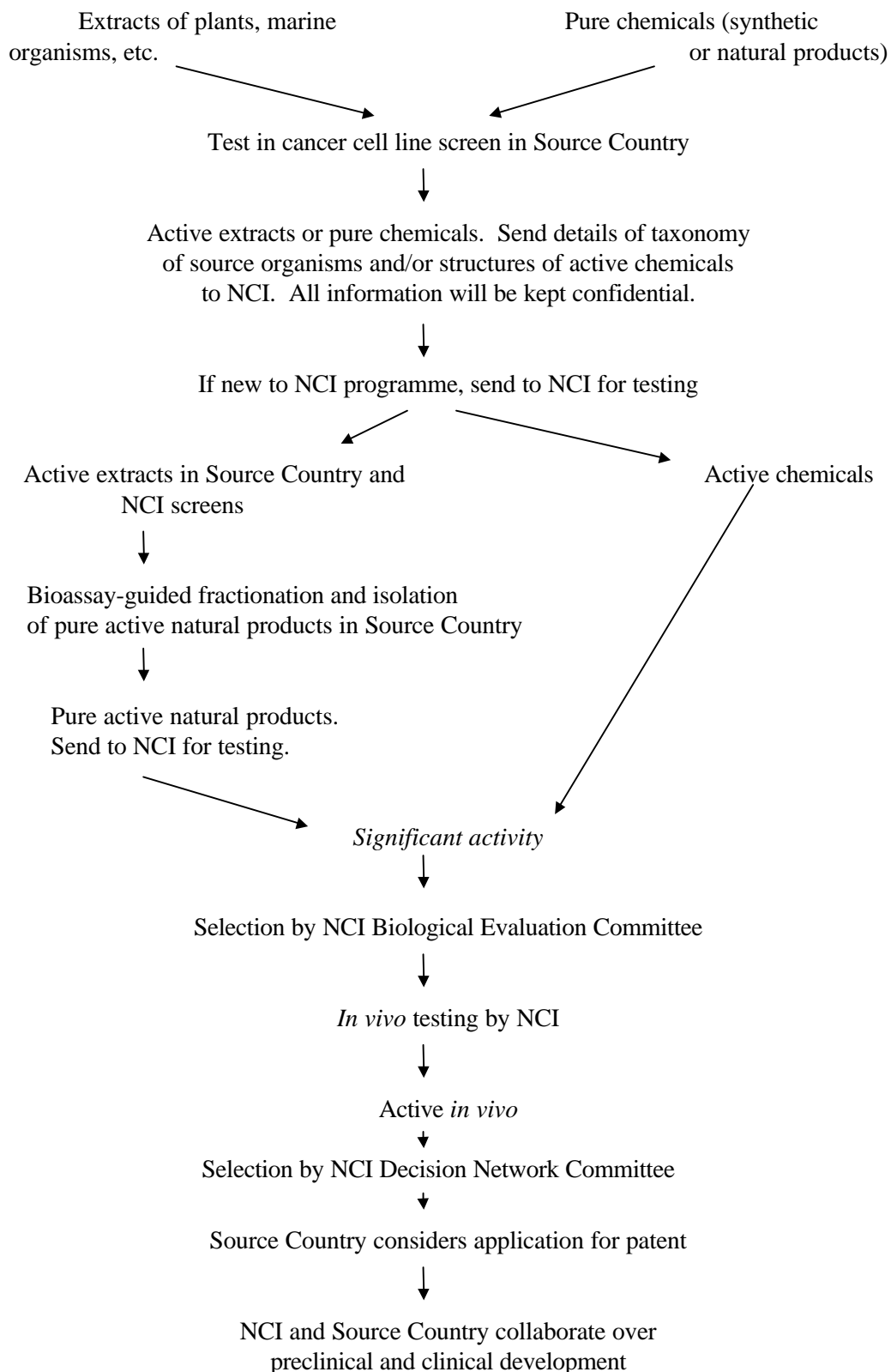
Researchers wishing to obtain samples from the NCI's Natural Products Repository (NPR), and who are

²³⁶ Personal communication between Dr Gordon Cragg, National Cancer Institute, 17 April, 1998.

²³⁷ Personal communication, Dr Gordon Cragg, National Cancer Institute, 17 April, 1998.

²³⁸ However, NCI's right extends only to patents using data generated by DTP laboratories and only to clinical trials, rather than to commercialisation. Personal communication, Dr Gordon Cragg, National Cancer Institute, 9 February 1998.

**COLLABORATION WITH THE NCI
UNDER THE MEMORANDUM OF UNDERSTANDING**



deemed eligible pursuant to NCI criteria,²³⁹ are obliged to sign the NPR's material transfer agreement (the NPR MTA) under which crude extracts and related confidential information is transferred to them.²⁴⁰ The recipients are entitled to evaluate the extracts but may not use them for commercial purposes such as production or sale, for which a separate license would be required, if such activities were to be allowed.²⁴¹ The license could be granted either pursuant to 35 USC 207 or, if the NCI and the recipient decide to engage in cooperative research and development using the material transferred, or if the recipient wishes to license intellectual property rights held by NCI, pursuant to a CRADA.²⁴² Further exchange of materials transferred by the recipient to other collaborating organisations may occur only upon execution of a copy of the NPR MTA by each such collaborator.²⁴³ Under the NPR MTA, the recipient also agrees not to transfer materials to others without the advance written approval of the NCI, although execution of the NPR MTA would constitute such approval *per se*.²⁴⁴

The terms of the NPR MTA require the recipient to acknowledge that the material it obtains from the NPR may have been acquired by the NCI under a Letter of Collection agreement with an authorised entity within the source country of such material. Whether or not this is the case, the recipient must also agree that, in the event that such material is eventually developed and marketed by the recipient, or licensed by the recipient to a third party for development and subsequent marketing, the recipient or the recipient's licensee will negotiate and enter into an agreement with the appropriate entity in the source country of such material. Under the terms of the NPR MTA, negotiations on this agreement must commence prior to the start of clinical development studies, and must be completed, and the agreement executed, prior to the commercial sale of any product based on such material. The NPR MTA further stipulates that the final agreement must address the mutual concerns of both parties, and that it must be binding upon both parties with respect to intellectual property rights.²⁴⁵

In addition to this requirement that the recipient (or its licensee, as appropriate) must enter into an agreement directly with a source country organisation, the NPR MTA specifically requires the recipient to use the source country as its first source of supply and cultivation for any raw materials that may be required for the manufacture of any product based on samples of those materials transferred by NPR to the recipient under the MTA, provided such material is readily available at a reasonable price.²⁴⁶ The terms of the NPR MTA also oblige the recipient to provide screening results to the NCI, a summary of which will be provided by NCI to the source country.²⁴⁷

As far as ownership rights are concerned, the terms of the NPR MTA provide that the NCI retains ownership over the materials being transferred to the recipient. However, intellectual property rights on inventions made by employees of the NCI or the recipient will be allocated depending on the principle of "inventorship", as determined by governing patent law.²⁴⁸

²³⁹ The National Products Repository (NPR) of the NCI's Development Therapeutics Program is a national resource containing materials, both those not currently under active investigation by the NCI and those which are, which are made available to the greater research community. The research selection criteria and procedures for selecting qualified research organisations to whom to provide NPR samples are outlined in Appendix A ("Policy for the Distribution of Materials from the Natural Products Repository") to the Model Natural Products Repository Material Transfer Agreement, Natural Products Branch, Developmental Therapeutics Program, Division of Cancer Treatment, Diagnosis and Centers, National Cancer Institute, National Institutes of Health, Last Revised and Approved by OTD/NCI and DCTDC/NCI on August 8, 1997. For more information see: <http://epnws1.ncicrf.gov:2345/dis3d/natprod/np_open.html>

²⁴⁰ Preamble, Model Natural Products Repository Material Transfer Agreement, Natural Products Branch, Developmental Therapeutics Program, Division of Cancer Treatment, Diagnosis and Centers, National Cancer Institute, National Institutes of Health, Last Revised and Approved by OTD/NCI and DCTDC/NCI on August 8, 1997.

²⁴¹ *Ibid.*, Clause 3.

²⁴² *Ibid.*, Clause 11.

²⁴³ *Ibid.*, Clause 3.

²⁴⁴ *Ibid.*, Clause 5.

²⁴⁵ *Ibid.*, Clause 9 (for the terms discussed in this paragraph).

²⁴⁶ *Ibid.*, Clause 9.

²⁴⁷ *Ibid.*, Clause 10.

²⁴⁸ *Ibid.*, Clause 8.