



NIPRISAN Case, Nigeria
A Report for *GenBenefit* (2007)

Prof. Charles Wambebe

International Biomedical Research in Africa, Garki POB 3359,
Abuja. Nigeria.



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1. Executive Summary

There is no standard therapy for sickle cell disorder (SCD) in Sub-Saharan Africa. Thus, most SCD patients resort to the use of herbal medicines. Consequently, the search for medicine for the management of SCD at the National Institute for Pharmaceutical Research and Development (NIPRD) focused on indigenous medical knowledge and indigenous biodiversity. The NIPRD received credible information about Rev. Ogunyale who was treating SCD patients with a herbal medicine. Professor Wambebe, who was the Chief Executive Officer of the NIPRD invited Rev. Ogunyale to discuss possible collaboration with him. As Rev. Ogunyale was educated in the USA (he has an M.Sc. degree in psychology), he understood the implications of this kind of collaboration. After some negotiations, he released his recipe, as a sacred trust, for further development into an effective medicine for the benefit of SCD patients globally. This paper will examine the negotiation processes involved in this project, and its outcomes, to assess if they comply with current international guidelines.

The first critical negotiation was the Memorandum of Understanding (MOU)¹. MOUs regarding a research collaboration between the NIPRD and a traditional health practitioner were new to the NIPRD in 1992 when the project commenced. At the time of the negotiations, neither the *Convention on Biological Diversity* (CBD)² nor the *Bonn Guidelines*³ had been adopted. What was clear to the NIPRD however was that an MOU was necessary so as to be transparent, fair and equitable and to serve as the legal basis for the research collaboration between the NIPRD and traditional health practitioners. Hitherto, traditional health practitioners did not tend to trust biomedical researchers, since similar collaborations in the past had not yielded acceptable outcomes. This was due to inappropriate, or complete lack of, negotiation on ownership and acceptable benefit sharing formulas. In order to enrich negotiations with the traditional health practitioners, the NIPRD contacted the World Intellectual Property Organisation (WIPO) which provided various resource materials. Prof Wambebe, was also given the opportunity to participate at relevant workshops on intellectual property rights (IPR). Based on this experience and resources, the MOU was developed with the assistance of an NIPRD Legal Adviser. Thereafter, the MOU was fully discussed with the traditional health practitioner. The traditional health practitioner was advised not to make an immediate decision until he had discussed matters with his family and lawyer, and the traditional health practitioner indeed returned to the NIPRD with some questions which resulted in further negotiations. This process can now be considered as obtaining prior informed consent. This paper will compare the process to the principles of the prior informed consent system as outlined in Article 15, paragraph 5 of the CBD and further elaborated in the *Bonn Guidelines*. The content of the MOU will be weighed against the *Bonn Guidelines* to identify any disparities.

The second critical decision in the process involved the issues related to the scientific validation of NIPRISAN (the trade name given to the herbal medicine by the NIPRD) which was derived from

¹ Wambebe, C. (1999). *Collaborative Agreement between the National Institute for Pharmaceutical Research and Development, Abuja, Nigeria and Holders of Traditional Medical Knowledge Intellectual Property and Expectations of Traditional Knowledge Holders*. World Intellectual Property Organization Report on Fact Finding Mission on Intellectual Property and Traditional Knowledge, Geneva.

² Convention on Biological Diversity (1992) At: <http://www.biodiv.org/doc/legal/cbd-en.pdf>, accessed: 31 July 2007.

³ Bonn Guidelines (2002) At: <http://www.biodiv.org/programmes/socio-eco/benefit/bonn.asp>, accessed: 31 July 2007.

Piper guineenses seeds, *Pterocarpus osun* stem, *Eugenia caryophyllum* fruit and *Sorghum bicolor* leaves⁴. The costing of the raw materials which would be supplied by the traditional health practitioner was then negotiated. The methodology which would promote adherence to World Health Organisation (WHO) Good Laboratory Practice was another critical milestone. The researchers needed to be trained in the application of good laboratory practice principles which were essentially alien to African scientists at that time.

The third critical decision related to the safety and efficacy investigations of NIPRISAN in SCD patients. A protocol for the study was developed, discussed and submitted to an Independent Ethics Committee for their consideration and approval. The Principal Investigators at the hospitals where the clinical trial would be conducted were appointed. Negotiations took place between the Independent Ethics Committee and the researchers. Subsequently, negotiations were necessary between the researchers, the investigators at the trial sites and the Hospital Ethics Committees. These negotiations resulted in appropriate changes to the study protocol and the standard operating procedures (SOPs) for the clinical trial, prior to decisions on the content of the clinical protocol.

Intensive negotiations took place over a period of time between researchers and the patent attorneys regarding the content and format of the patent document. According to Article 27 of Trade Related Aspects of Intellectual Property Rights (TRIPS) Agreement, patents can be granted in all fields of technology *vis-à-vis* processes and products. Although article 27.3(b) of TRIPS allows the exclusion of plants and animals from patentability, article 27.1 contains universally accepted criteria for patentability viz; novelty, non-obviousness and applicability or utility. Thus, the caveat that natural substances do not qualify for patentability applies directly to plants, animals and micro-organisms, whereas the technical processes applied to develop a product with a potential for future commercialization for specific public use can be patented. The patenting of NIPRISAN in the USA was undertaken under this premise.⁵ At the end of the negotiations, specific decisions were made regarding the content of the patents.

The negotiations regarding publication policy were carried out during the formulation of the MOU. The negotiations regarding granting the company the exclusive license for the production and global marketing of NIPRISAN involved the NIPRD, the Federal Ministry of Health and the potential investor; XECHEM International Inc., (XECHEM). Eventually, the decision was made to grant XECHEM the license with a provision of 7.5% of total sales as royalties, and a good faith payment. This paper will examine the extent to which the relevant stakeholders were involved in the negotiations as well as the comprehensiveness and fairness of the provisions of the License to the relevant stakeholders in relation to international guidelines.

A ceremony to mark this remarkable event, the first of its kind in Africa involving the transfer of medicine fully developed in Africa, by African scientists, to the Western world, took place on July 18, 2002. The President of the Federal Republic of Nigeria, Olusegun Obasanjo, personally launched NIPRISAN after it had been registered by the National Agency for Food and Drug Administration

⁴ Wambebe, Charles (2006). "From Plants to Medicine for Management of Sickle Cell Disorder," Guest Editorial: *Innovation and Discovery*, vol. 18 (1) pp1-4.

⁵ Wambebe, C., Ogunyale, P.O., Gamaniel, K.S., Nasipuri, R.N., Okogun, J.I., Samuel, B., Olusola, A. and Orisadipe, A. (1998). *Piper guineensis, Pterocarpus osun, Eugenia caryophyllum and Sorghum bicolor extracts for treatment of sickle cell disease*. United States Patent No 5,800,819 of September 1998.

and Control on July 6, 2006. The uniqueness of the NIPRISAN case is that the project was initiated and executed by African scientists working in Africa at a time when international provisions for benefit sharing regarding commercial products derived from indigenous medical knowledge were unavailable. It will be interesting to analyse the benefit sharing elements of the MOU developed by the NIPRD for research collaboration with traditional health practitioners against currently available international provisions and examples. Are there elements of the benefit sharing formula contained in the MOU and the subsequent exclusive License granted to XECHEM Inc. which could be considered for inclusion/exclusion in a benefit sharing check list?

2. Introduction

SCD is the silent killer of infants in Sub-Saharan Africa. The prevalence of SCD is estimated at over 2% while about 25% of the general population in Sub-Saharan Africa have sickle cell traits.⁶ Infant mortality is about 8% and the survival rate of SCD babies in rural areas by five years of age is about 20%.⁷ Presently, only palliative management measures are available in the health sector for SCD patients in Africa. Consequently, most SCD patients die early from microbial infections, malaria and SCD related complications. Undoubtedly, SCD is a major public health problem in Sub-Saharan Africa where it is endemic. Those who survive early childhood mortality suffer from cycles of excruciatingly painful crises, interrupted educational careers and social discrimination. For the 12 years Wambebe served as the Pioneer Chief Executive Officer of the NIPRD (CEO), SCD was the priority disease targeted for development of new medicines.

There are various recipes for the management of SCD patients in Sub-Saharan Africa. However, the NIPRD chose to work with Rev. Ogunyale to research and develop his recipe through the application of modern science and technological tools based on credible ethnomedical use. The unique features of this case study include the MOU between the traditional health practitioner and the NIPRD, which includes provisions for the traditional health practitioner as a viable member of the research team, improvement of the recipe the traditional health practitioner used at his clinic, payment of an honorarium, and publication and patent policies. Furthermore, the license agreement indicates royalties of 7.5% of gross sales as well as to a good faith payment of \$115,000. In addition, the establishment of a drug manufacturing facility at Abuja by XECHEM will create jobs for Nigerians, build capacity, generate wealth for the economy and promote the development of other herbal medicines based on indigenous medical knowledge. Thus, the formulation of policies on benefit sharing on genetic resources may be able to usefully adopt some provisions of the MOU and license agreement.

It is vital that there is a 500-fold difference between the highest dose used in the toxicity studies and the clinically effective dose, indicating a very high therapeutic index for NIPRISAN.⁸ According to the WHO, when there is evidence of long term use of a traditional medicine product, the most crucial

⁶ Lesi F.E.A. (1999). *Sickle Cell Disorder: A Handbook for Patients, Parents, Counselors and Primary Health Care Practitioners*. Nigeria, Macmillan, pp1-10.

⁷ Effiong, C.E. (1982). *Sickle Cell Disease in Childhood: A Handbook for the General Clinician*. Edited by A.F. Fleming, Churchill Livingstone Publishers, London, pp 1-23.

⁸ Wambebe, C. et al (2001). "Double-blind, placebo-controlled, randomized, cross-over clinical trial of NIPRISAN in patients with Sickle Cell Disorder," *Phytomedicine*, volume 8 (4), pp 252-261.

criterion for its assessment is the safety profile.⁹ Thus, the high therapeutic index of NIPRISAN regarding its safety profile conforms to WHO requirements. The pharmacological profile of NIPRISAN in animals supports its observed clinical effects. Phytochemical screening of the four plants used in the formulation of NIPRISAN was also undertaken. It was observed that NIPRISAN reversed sickled red blood cells and protected them from being sickled when exposed to low oxygen tension – thus providing scientific evidence for its therapeutic use. NIPRISAN dose-dependently delayed polymer formation of hemoglobin S, which demonstrates additional evidence for the clinical use of NIPRISAN.

In accordance with international practice, an appropriate clinical protocol was developed and subjected to ethical review.¹⁰ The Independent Ethics Committee considered and approved the protocol prior to the commencement of the clinical trial. Furthermore, approval was obtained from National Agency for Food and Drug Administration and Control. Consent and patient information forms were developed in conformity with WHO requirements and used for the clinical trials.

The clinical trials were conducted at the NIPRD Clinic, Abuja and Military Hospital, Yaba, Lagos. The data indicated that all the subjects benefited from NIPRISAN with no serious adverse effects. About 80% of the subjects did not experience any crisis during the period of the study, while the remaining subjects had less severe and less frequent SCD-related crises. The subjects experienced significant reductions in hospital admissions, while attendance at school was profoundly increased¹¹.

3. Memorandum Of Understanding.

The MOU developed by the NIPRD for research collaboration with traditional health practitioners was unique. It was regarded as the first of its type globally and has therefore been adopted by both WIPO¹² and WHO.¹³ Developing countries have recently argued persuasively on the issue of biopiracy and the need to address this by linking it to the TRIPS Agreement.¹⁴ This political thrust is based on the allegation that some Northern companies pirate and patent biological materials and traditional knowledge as a deliberate policy without engaging in the fair and equitable sharing of benefits, which is against CBD provisions for equity. This collaboration aimed at establishing a legal basis for the scientific and clinical assessments of herbal medicines based on the indigenous medical

⁹ World Health Organization (2000). *General Guidelines on Research and Evaluation of Traditional Medicine*. Geneva, WHO/EDM/TRM/2000.1

¹⁰ ICH Secretariat (1997). *International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use*, Geneva.

¹¹ Wambebe, C. (2001). Double-blind, placebo-controlled, randomized, cross-over clinical trial of NIPRISAN in patients with Sickle Cell Disorder. *Phytomedicine*, volume 8(4), pp252-261.

¹² Wambebe, C. (1999). *Collaborative Agreement between the National Institute for Pharmaceutical Research and Development Abuja, Nigeria and Holders of Traditional Medical Knowledge Intellectual Property and Expectations of Traditional Knowledge Holders*. World Intellectual Property Organization Report on Fact Finding Mission on Intellectual Property and Traditional Knowledge

¹³ World Health Organization (2004). *Model Agreement between Research Institutes and Traditional Health Practitioners*. In: Generic Model Guidelines for Clinical Study of Traditional Medicine in WHO African Region. WHO/EDM/TRM/2004.4

¹⁴ Watal, J. (2005). "Intellectual Property and Biotechnology: Trade Interests of Developing Countries," in: *Trading in Genes : Development Perspectives on Biotechnology, Trade and Sustainability*. Edited by Ricardo Melendez-Ortiz and Vicente Sanchez, pp123-127, Earthscan Publications Ltd, London.

knowledge of traditional health practitioners. In essence, the MOU served as prior informed consent for the NIPRISAN project. According to article 15, paragraph 5 of the CBD, prior informed consent is a requirement for access to genetic resources. Legal clarity and certainty is one of the basic principles of the prior informed consent system. However, since the MOU was drafted using legal language, it may not be transparent to a layperson. Furthermore, it should be noted that the potential impact on conservation issues and the sustainable use of biodiversity were not addressed in the MOU, which should be corrected by any organization adopting it in the future.

The importance of adhering to standard procedures in the administration of prior informed consent is evident in the case of the Kani tribe from South Western India.¹⁵ The indigenous medical knowledge of the Kani tribe indicated that a local plant, *Trichopus zeylanicus*, possessed anti-fatigue properties. A herbal medicine, called Jeevin, was developed from the plant by the Tropical Botanic Garden and Research Institute (TBGRI), while the manufacturing license was granted to Aryavaidya Pharmacy for \$25,000.00. TBGRI agreed to share the license fee and royalties equally with the Kani tribe. Members of the Kani tribe located in different areas also want to be included in the benefit sharing formula. The Agreement should be commended for the provision regarding sharing the license fee and royalties equally between the institution and the Kani tribe.

Based on the MOU, the traditional health practitioner is expected to disclose all plant collections related to the treatment of the particular disease which constitutes the subject of the collaboration. Furthermore, complete disclosure on the ethnomedical use, botanical identification, method and timing of collection, processing, packaging and dosage is required.

It is the responsibility of the NIPRD to scientifically and clinically evaluate the herbal medicine regarding its safety and efficacy. It is also the responsibility of the NIPRD to adhere to the highest ethical standards in the conduct of their research activities and to report the outcomes of their findings to the traditional health practitioner. The responsibility of the traditional health practitioner is to provide all the raw plant materials required for the project. The NIPRD paid the traditional health practitioner for the plant materials supplied, transport costs, and an accommodation allowance during visits to the institution to deliver the materials.

Although the NIPRD's MOU was developed about 10 years before the adoption of the *Bonn Guidelines*, it is relevant to assess the extent to which its four requirements for mutually agreed terms were fulfilled¹⁶.

The first requirement is the use of resources, taking into account the concerns of the particular parties, in this case, the traditional health practitioner. A critical concern of the traditional health practitioner is recognition as an active team player. The inclusion of the traditional health practitioner as a member of the Research Team, assigning him the responsibility to supply all the raw plant materials fulfils the concern of the traditional health practitioner.

¹⁵ Kerry ten Kate & Sarah A Laird (1999). *The commercial use of biodiversity: Access to genetic resources and benefit sharing*, pp.29, Earthscan Publications Ltd, London.

¹⁶ Secretariat of the Convention on Biological Diversity (2002). *Bonn Guidelines on Access to Genetic Resources and Fair and Equitable Sharing of the Benefits Arising out of their Utilization*, Section D, paragraph 43, a-d.

The second requirement concerns the continued customary use of genetic resources and related indigenous medical knowledge. The MOU allows the traditional health practitioner to continue to use his recipe based on his indigenous medical knowledge. In fact, the NIPRD improved his capacity for standardization of his product. On the other hand, the NIPRD changed the recipe based on the outcome of research findings for further development into NIPRISAN.

The third requirement regarding joint research obligations is contained in the MOU as evidenced by the inclusion of the traditional health practitioner as an author of all publications on NIPRISAN emanating from the NIPRD. The second arm of the third requirement relates to provision of licenses by common consent. Unfortunately, the traditional health practitioner was not involved in the negotiations leading to the licensing of NIPRISAN to XECHEM. Furthermore, the principal investigator of the research and development of NIPRISAN (Prof Charles Wambebe) was not actively involved in the negotiations on the license.

The last requirement concerns “the possibility of joint ownership of IPR according to the degree of contribution”. This requirement was only partially fulfilled. The traditional health practitioner and the researchers were included in the patent document. However, to date neither the traditional health practitioner nor the researchers have received any monetary benefit from the NIPRD in spite of the fact that XECHEM has paid \$115,000 (one-off good faith payment) plus the first royalty to the institution. In fact, Article 8(j) of the CBD has provision for the equitable sharing of benefits arising from the knowledge, innovations and practices of indigenous and local people. The CBD however only indicates the equitable sharing of benefits “as far as possible¹⁷.” Understandably, it does not stipulate a specific formula, and the sharing of benefits equitably “as far as possible” is open to different interpretations. In view of this background, coupled with the fact that most developing countries lack national legislation on bioprospecting, only a few companies voluntarily share benefits equitably in return for access to genetic resources and indigenous medical knowledge.¹⁸ However, in the NIPRISAN case, the company (XECHEM) has so far promptly fulfilled its obligations regarding payments of license fees and royalties to the NIPRD. It is the latter that has so far not shared such monetary benefits with the traditional health practitioner and the researchers.

The MOU can be terminated if the traditional health practitioner commits a deliberate breach of any of the terms of the MOU which he refuses to rectify, even upon demand. Similarly, the MOU can be terminated if the NIPRD fails any of its obligations to the traditional health practitioner, or fails to evaluate the plant material used to prepare a specific medicinal product in accordance with the specific recipe. According to the MOU, if any dispute arises as to the implementation of the terms, the parties shall either appoint one independent Arbitrator or constitute a panel of three Arbitrators.

Lastly, the MOU guarantees the equitable sharing of benefits arising from the economic potential of new medicines based on indigenous medical knowledge. As indicated above, this provision has not yet been implemented by the NIPRD. The traditional health practitioner is entitled to a 10% royalty

¹⁷ Convention on Biological Diversity, Article 15.7 (1992). At: <http://www.biodiver.org/doc/legal/cbd-en.pdf> , accessed on 31 July 2007.

¹⁸ Otten, A (1994). “*The Uruguay Round TRIPS Agreement : Implications for the protection of plant varieties,*” presentation at the workshop on Intellectual Property Rights in Relation to Agricultural and Microbiological Biotechnology, Madras, 7 March.

(in perpetuity) of profits generated by the sale of any commercialized product. Patenting of the product and the preservation of indigenous medical knowledge are non-financial benefits to all the stakeholders (i.e. SCD patients, Government, the NIPRD, XECHEM Inc., traditional health practitioner and researchers). SCD patients will benefit from the use of NIPRISAN as the only prophylactic agent available to them in Africa. The economy of Nigeria will also benefit from this investment, especially with the establishment of a drug manufacturing facility at Abuja. The company claims that when in full production, the market for NIPRISAN will be worth over \$1 billion a year. The NIPRD will benefit from the royalties (7.5% of gross sales). A separate MOU is envisaged to be developed which will indicate the benefit sharing formula between the traditional health practitioner, researchers and the NIPRD, thereby benefiting all the stakeholders.

3. Testing NIPRISAN in Clinical Trials

The first issue relates to the use of the bio-active compound for further development into a marketable medicine. The two bioactive compounds so identified are vanillin¹⁹ and 5 hydroxy methyl furfural²⁰. The fact that the total extract manifested more bioactive property than the single compound guided us to use the former. The highest dose used in the animal studies, which failed to elicit toxic symptoms is about 500 times higher than the effective clinical dose. This wide gap between the clinically effective dose and the toxic dose (high therapeutic index) provides a strong ethical basis to evaluate NIPRISAN in humans without compromising on the safety and well being of the trial participants.

The efficacy studies indicate that NIPRISAN improved oxygenation of these animals and protected them from death in a dose dependent manner when they were exposed to low oxygen tension. Since SCD patients can die from acute chest syndrome without warning, it is significant that NIPRISAN prevents such sudden deaths in animals, thereby providing a scientific basis to use NIPRISAN as a prophylactic medicine²¹.

Three separate clinical trials were conducted using NIPRISAN and SCD patients. The clinical data from these three trials are in agreement with one another. All three studies clearly demonstrate an improvement in the quality of life of all study participants, thereby providing ethical justification for the use of NIPRISAN in humans.

A research team comprising the heads of departments of all the relevant disciplines required for the program was established, with the CEO of the NIPRD as principal investigator. Prior to recognizing SCD as the top priority disease which would be targeted for drug development, the CEO delivered a seminar on its epidemiology. Subsequently, each department developed their work plans for this program. Such action plans were then discussed by the institute's sickle cell research team.

Good laboratory practice (GLP) guarantees the generation of reliable observations that can be reproduced anywhere in the world under similar experimental conditions. The documentation of all processes and observations is a cardinal practice in GLP. The general objective is to validate the

¹⁹ Wambebe, C. (2001). Unpublished data.

²⁰ Pandey, R. (2006). Personal communication.

²¹ Iyamu, E.W, Turner, E. and Asakura, T. (2003). NIPRISAN (Nix-0699) improves the survival rates of transgenic sickle cell mice under acute severe hypoxic conditions. *British Journal of Hematology*, Volume 122, pp 1001-1008.

claims of traditional health practitioners by applying modern science and technological tools and methodologies. The challenge in traditional medicine research is the profound variabilities in the constituents of plants. The factors responsible for these variabilities include the age of the plant at time of harvesting, the season of the year, the ecological location of the plants, the time of the day that the plant samples are collected as well as the post-harvesting processes. The variabilities, if not properly controlled, would ultimately affect the therapeutic benefit derivable from the product. Thus, each of the factors indicated above have to be properly standardized so as to guarantee consistency in the therapeutic outcomes of NIPRISAN. The study design included blinding of the clinicians, patients and the statistician.

The principal investigators were selected for the study based on their qualifications and relevant experience. They were initially approached to acquaint them with the responsibilities that would be assigned to them and given copies of the protocol in advance. Subsequently, discussions were held to clarify issues from the protocol. The formulation was difficult and involved modifications of various pharmaceutical technical properties. The purpose was to employ processes in formulating NIPRISAN into a dosage regimen that would promote compliance, in a capsule dosage form which would not interfere with the intended therapeutic outcome. It is good scientific practice to determine the criteria for efficacy prior to commencement of the study. In this case, the efficacy criteria included number of crises, effects on hospital visitation/hospitalization and effects on school attendance²². The safety profile was also a major component of the efficacy criteria. The effect on the quality of life of the patients constitutes a critical factor. The criteria for safety include the scores on Karnofsky performance and toxicity grading scales²³.

The crucial factors considered for the development of the protocol are the rights of the patient, and their well being and safety, in accordance with international practice.²⁴ The ethical concerns regarding the well being of the patient were guaranteed in the protocol through the provision of adequate care throughout the duration of the trial in accordance with national treatment standards. The rights of patients are also enshrined in the protocol by allowing patients to withdraw from the trial at any time without jeopardizing the standard of care they are entitled to. With respect to the safety of the patients, the data on the observational study was explained to them. The data indicated that no patient had manifested any serious adverse effect. In addition, the clinician in charge of the study was empowered in the protocol to withdraw any patient who was not responding to NIPRISAN or who developed any serious adverse effects.

At the time the study of NIPRISAN began in 1992, the National Agency for Food and Drug Administration and Control did not have regulations on the clinical evaluation of herbal medicines, but the NIPRISAN case adhered to WHO approved procedures regarding the development of new medicines. After obtaining the approval of the Independent Ethics Committee, regulatory clearance for the conduct of the clinical trials was requested and obtained from the National Agency for Food and Drug Administration and Control.

²² Wambebe, C. et al (2001). Double-blind, placebo-controlled, randomized, cross-over clinical trial of NIPRISAN in patients with Sickle Cell Disorder. *Phytomedicine*, volume 8(4), pp252-261.

²³ World Health Organization (2004). *Generic Model Guidelines for Clinical Study of Traditional Medicines in the WHO African Region*. WHO/EDM/TRM2004.4

²⁴ Council for International Organizations of Medical Sciences (2002). *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. CIOMS, Geneva.

Since NIPRISAN was developed at the NIPRD, Independent Ethics Committee approval was preferred to Institutional Review Board. A research fellow from the NIPRD was seconded to the Independent Ethics Committee to provide the necessary information required by the committee, but this individual had no voting rights. Prior to instituting the committee, individual meetings were held with the prospective members to obtain their prior consent to serve. During these meetings, the members had an opportunity to seek clarification regarding their roles, as well as data on NIPRISAN.

Informed consent is the process by which a fully informed patient can participate in choices about their health care.²⁵ It is a functional process that begins prior to the commencement of a particular study and continues until the end. It is a consequence of the legal and ethical rights the subject has to be fully involved on matters that pertain to their well being and health. In order to be fully informed, it is implied that the language of communication is fully understood by the subject.

As per WHO guidance, two instruments for obtaining prior informed consent (patient information sheet and informed consent) were used²⁶. The major purpose of informed consent is to fully acquaint the patients with the study that will be undertaken, stressing that their rights, safety and well being will be guaranteed if they decide to take part. A patient information sheet was used here, which describes in simple language the procedures involved in the clinical trial. It also describes the anticipated risks and benefits of the new medicine. The clinical protocol makes provision for any subject to withdraw from the study at any time without any penalty. Thus, the standard process for undertaking informed consent was carefully adhered to in the NIPRISAN case.

4. Negotiations and Decision Making Processes

With the traditional health practitioner

In order to obtain the cooperation of the traditional health practitioner to disclose his recipe, his prior informed consent was fundamental to the whole drug development chain. The negotiation required for obtaining prior informed consent was made easier because Rev. Ogunyale and Prof. Wambebe share a common faith which facilitated the development of mutual trust. During this original process, Rev. Ogunyale was briefed on what needed to be done, how it would be done and why. In addition, the responsibilities and benefits relating to him, the NIPRD and SCD patients were explained.

Negotiations were held with the traditional health practitioner on the cost per kg of the samples, the physical state of the samples as well as the frequency of supplies and the terms of payment. The quantity of the samples varied at different stages of the research and development of NIPRISAN. The quantities increased as the project progressed from purely research components to more developmental aspects. Negotiations involved the transport fare, a subsistence allowance and small honorarium for each trip to the NIPRD by the traditional health practitioner. The main purpose of involving the traditional health practitioner in sample collection is to ensure that the traditional health practitioner is part of the research team and is aware of the various stages in the research and

²⁵ *Ethics in Medicine*. University of Washington School of Medicine, <http://depts.washington.edu/bioethx/topics/consent.html>, accessed on 15 July 2007.

²⁶ World Health Organization (2004). Generic Model Guidelines for Clinical Study of Traditional Medicines in WHO African Region. WHO/EDM/TRM/2004.4

development of the product. The NIPRISAN case assumes that such provision contributes to equity and that sharing of responsibilities leads to joint ownership.

Developing The MoU

“Northern firms have been accused of pirating and patenting genetic resources and indigenous medical knowledge of gene-rich developing countries for profit without fair and equitable sharing of benefits or appropriate transfer of the new technologies as demanded by the Convention on Biological Diversity”²⁷. To the best knowledge of the NIPRD at the time this study began in 1992, there was no model of any MOU for collaboration between scientists and traditional health practitioners. The goal of the MOU was to establish a legal basis for the research collaboration with clear provisions on the responsibilities of the parties involved, the potential benefits, and a formula for equitable benefit sharing of any commercial product arising from the collaboration. The stakeholders (i.e. the NIPRD, the National Agency for Food and Drug Administration and Control, traditional health practitioner, researchers and SCD subjects) were separately and clearly informed about the programme. Meetings were held at various stages of the programme with different stakeholders to negotiate and agree on the procedures and issues involved in the whole process. The instruments for implementation differ among the various stakeholders. In the case of the traditional health practitioner, the instrument for implementation was the MOU. On the other hand, the instrument for implementation with respect to the patients is the clinical protocol for the study. With regards to the regulatory agency, there are two main instruments; the clinical protocol for the trial and the signed copy of the approval by the Independent Ethics Committee. Unfortunately, during the NIPRISAN case, the National Agency for Food and Drug Administration and Control was newly established and had as yet no regulations which would have involved the agency in regulatory inspections of the clinical trial centres.²⁸

National and International

The resources required for research and development of medicines are immense. Negotiations were undertaken for resource mobilization within the government and through international organizations. The negotiations with the government generally involved allocation of special grants to the NIPRD for the programme which are outside the regular budgetary allocations. Such special government grants amounted to about \$7 million during the 10 year period of developing NIPRISAN. Negotiations for a Japanese grant through a bilateral agreement yielded \$3.5 million. The last major negotiation was with the United Nations Development Program (UNDP). The NIPRD’s proposal won the competition on merit basis with a grant of \$1.65 million. The human resources for this programme were recruited locally. Most of them had already obtained PhD or MSc degrees in their various fields. Training programs were organized for the research fellows, mainly in United Kingdom, Switzerland, India and Germany.

²⁷ Watel, J. (2005). Intellectual Property and Biotechnology: Trade Interests of Developing Countries. In: *Trading in Genes; Development Perspectives on Biotechnology, Trade and Sustainability*. Edited by Ricardo Melendez –Ortiz and Vincente Sanchez. Earthscan Publications Ltd, London, PP123-124.

²⁸ The National Agency for Food and Drug Administration and Control now has appropriate regulations which guarantee such regulatory inspections.

Patenting & Licensing

NIPRISAN was patented first in Nigeria and later in the USA and 46 other countries. The negotiations involved the NIPRD and the patent lawyers. The patenting of NIPRISAN in Nigeria and the USA was carried out by the NIPRD using its own resources, while the UNDP was responsible for patenting in 46 other countries. The negotiations regarding patenting of NIPRISAN were undertaken between the NIPRD and the Nigerian Patent Office. The patenting of NIPRISAN in the USA involved the use of patent lawyers and negotiations between the NIPRD and the patent lawyers. These negotiations only involved the UNDP, the NIPRD and the patent lawyers – both the traditional health practitioner and the SCD patients who participated in the study were excluded from the negotiations. Although the traditional health practitioner was included in the patent document, it is now recognized that it was inappropriate to have excluded him from the negotiations. The exclusion of the SCD study participants from negotiations regarding patenting of NIPRISAN is understandable. However, in retrospect, the license should have made provision for supply of NIPRISAN to the study participants for life, either free, or at a much reduced fixed rate that any of them could afford, for example \$1.00 per month supply. In fact, access of patients to the medicine in which they were used as study participants is enshrined in the Declaration of Helsinki²⁹.

In 2004, the United States Food and Drug Administration granted orphan drug status to NIPRISAN. This recognition guarantees an accelerated processing of the dossier for registration of NIPRISAN in the USA. Similarly, the European Medicine Evaluation Agency granted orphan drug status to NIPRISAN in 2005.

Negotiations were undertaken between the NIPRD, the Federal Ministry of Health and XECHEM Inc. Subsequently, the license agreement was drafted based on the negotiations. The processes involved in these negotiations were cumbersome and lengthy. XECHEM demonstrated optimism, patience and a quick understanding of the Nigerian system. On 18th July 2002 XECHEM was eventually granted an exclusive license for the manufacture and global sale of NIPRISAN. Following the successful negotiations between XECHEM, the Federal Ministry of Health and the NIPRD, the lawyers were briefed. The resulting legal drafts were studied by the three stakeholders. Further negotiations ensued leading to the final legal document. The agreed good faith payment was \$115,000.00 while the royalty on gross sales is 7.5%. According to Kate and Laird,³⁰ the average rate of royalties, if clinical data is provided, is between 5-15% of net sales. Thus, the agreed royalties for the NIPRISAN case are within the global practice range.

The application dossier for registration of NIPRISAN was compiled carefully and in detail as per the guidelines provided by the National Agency for Food and Drug Administration and Control. Upon receipt of the application for registration of NIPRISAN from XECHEM Nig. Ltd, the National Agency for Food and Drug Administration and Control initiated a meeting of stakeholders to discuss issues regarding the application. The principal investigator for the research and development of NIPRISAN was given a draft license document for review, but none of the key modifications suggested by the principal investigator were reflected in the final document, for example, a benefit

²⁹ World Medical Association Declaration of Helsinki (2000), Article 30; *Ethical Principles of Medical Research Involving Human Subjects*, First adopted in 1964 (Helsinki, Finland), subsequent revisions in 1975 (Tokyo, Japan), 1983 (Venice, Austria), 1989 (Hong Kong), 1996 (Somerset-West, South Africa) and 2000 (Edinburgh, Scotland).

³⁰ Kerry ten Kate and Sarah A. Laird (1999). *The Commercial Use of Biodiversity: Access to Genetic Resources and Benefit Sharing*, Earthscan Publications Ltd, London, p68.

sharing formula for the key stakeholders, and the establishment of a Trust Fund where all the payments would be lodged. The meetings held between the NIPRD and XECHEM Inc. deliberately excluded the researchers and the traditional health practitioner, and five years after signing the license agreement neither the researchers nor the traditional health practitioner have received any portion of the payment which was made to the NIPRD.

5. Evaluation of the Benefit Sharing Component in the License Agreement

The legal instrument for enforcing the provisions of the Agreement *vis-à-vis* benefit sharing issues is the License Agreement itself. According to Article 15, paragraph 7, of the CBD, each Contracting Party shall “take legislative, administrative or policy measures as appropriate with the aim of sharing in a fair and equitable way the results of research and development and the benefits arising from the commercial and other utilization of genetic resources with the Contracting Party providing such resources. Such sharing shall be upon mutually agreed terms.”

The license agreement is generally fair to both parties, but there are provisions which might have improved the benefits to the SCD subjects in Nigeria, SCD trial participants, the traditional health practitioner and the researchers.

The negotiating skills available to XECHEM Inc. and the NIPRD differ. Due to the high cost of establishing the XECHEM drug manufacturing facility at Abuja and additional development works on NIPRISAN, the present cost of NIPRISAN is not affordable to poor SCD patients. The SCD trial participants should have received free quantities of NIPRISAN for life since they were used to generate valuable clinical data, and a provision in the license regarding the cost of NIPRISAN would have been appropriate. However, the Government can consider purchasing regular quantities of NIPRISAN for free or subsidized rates to the public.

The royalty at 7.5% of gross sales is quite fair. The license deliberately excluded the proportion of the good faith payment and royalties that accrue to the traditional health practitioner and the researchers. Indeed, both the traditional health practitioner and the principal investigator were excluded from the negotiation process thus there was no opportunity to discuss details which might have culminated in mutually agreed terms. The provision for production of NIPRISAN in Nigeria and the USA is fair, and the whole agreement is subject to the laws of Nigeria and the USA. It appears that the benefit package of different benefits and the high royalty value is a reflection of the value added to NIPRISAN through the application of modern science and technological tools in its development. The license is crafted to meet the immediate expectations of the NIPRD and XECHEM Inc. The community where Rev. Ogunyale lived should also have benefited from the commercialization of NIPRISAN. Although the indigenous medical knowledge regarding the recipe for treating sickle cell disorder was a family secret and not a community knowledge, in virtue of their status as indigenes of Oyo town, it would have been appropriated to establish a health centre, school and medicinal plant farm. Such a farm would be used to cultivate the plants used for preparation of NIPRISAN. Consequently, the community would derive direct benefits from the indigenous medical knowledge of their fellow community member.

Perceptions of success therefore differ depending on the stakeholder. At the level of Government, transfer of NIPRISAN to the developed world is a major breakthrough with a multiplier effect on the

economy. Furthermore, the establishment of a drug manufacturing facility at Abuja by XECHEM Inc. to produce commercial quantities of NIPRISAN for the global market contributes to industrial development and is in consonance with the National Economic Empowerment Development Strategy (NEEDS). NEEDS is the foremost policy of Government. In the case of the traditional health practitioner, two issues are crucial for measuring success *viz*; the number of people using NIPRISAN in different countries, and the financial returns to the Ogunyale Foundation. At the time we knew Rev. Ogunyale, he was already old. He therefore established Rev. Ogunyale Foundation where all proceeds from the commercialization of his indigenous medical knowledge would be deposited. The Board of the Foundation would administer such Funds according to the constitution of the Foundation. Rev. Ogunyale died in 2002.

Post-market surveillance confirming the safety and efficacy of NIPRISAN will reaffirm the scientific credibility of the NIPRD's work. In addition, payment of the royalties would encourage the researchers and the NIPRD to apply the same methodology in developing other medicines. On the other hand, XECHEM's perception of success is the volume of sales globally. The adoption of appropriate policies by various governments in Africa (where SCD is endemic) regarding regular annual bulk purchase of NIPRISAN for free distribution or at heavily subsidized rates to the majority of SCD patients would be regarded by XECHEM Inc. as a major success.

Ordinarily, the benefits should have been shared equitably and fairly with all those who actively participated in the research and development of NIPRISAN, possibly through the establishment of a Trust Fund jointly administered by the stakeholders.

7. Conclusion and Lessons Learned

The cultivation of a vision with an accompanying strategy for implementation is an important lesson learnt. The most enduring component of the programme is the strengthening of research capacity. Collaboration with national and foreign universities and research institutes have provided unique opportunities for on-the-job and postgraduate training. In addition, various skills have been acquired including equipment maintenance, standard operating procedures, clinical trial management, pilot scale up, process technology, pilot drug production, etc. The NIPRD learnt that the development of a realistic MOU with the traditional health practitioner provided a basis for him to trust and collaborate with the researchers. The NIPRD acquired valuable experience on patenting and licensing to the private sector. The NIPRD also gained experience in proposal development for funding from Government, bilateral arrangements, United Nations agencies and international bodies. The aforementioned non-monetary benefits relating to the research and development of NIPRISAN and its subsequent commercialization are desirable and should be considered for inclusion in a standard benefit sharing check list.

The research and development of NIPRISAN based on indigenous medical knowledge using indigenous biodiversity has demonstrated their immense potential, thereby justifying further investigations based on African traditional medicine. According to XECHEM Inc., NIPRISAN has a global market of billions of dollars, and there will be multiple returns on the investment in the medicine to the traditional health practitioner, the NIPRD, the researchers and the Nigerian economy. The registration of NIPRISAN by the National Agency for Food and Drug Administration and Control has added to its global therapeutic profile, with the potential for significantly improving the

quality of life of SCD patients world-wide. The licensing of NIPRISAN to an American company has demonstrated the first case of reverse transfer of medical technology (medicine) in Africa. Such private-public partnership arrangements should be encouraged. The decision by XECHEM Inc. to establish a functional modern pharmaceutical manufacturing facility at Abuja to produce NIPRISAN in Nigeria for the global market is commendable. Such an action has obvious positive impacts on the Nigerian economy, capacity building, and foreign earnings and serves as a good example of a private-public partnership arrangement which should be contained in a benefit sharing check list.

The royalties associated with the licensing of NIPRISAN will stimulate research in indigenous medical knowledge and biodiversity in Africa. The MOU developed by the NIPRD for research collaboration with traditional health practitioner has been adopted by both the WHO and the WIPO. It is recommended that it be adapted appropriately for similar research collaborations. The content indicators for licensing agreements should be fully considered in future while all of the key stakeholders should be actively involved in all of the negotiations. In the NIPRISAN case, the key stakeholders who should have been actively and fully involved in all the negotiations are: the NIPRD; the Federal Government (owner of the NIPRD); XECHEM Inc (the company offered the exclusive License of NIPRISAN); the traditional health practitioner and the pioneer research fellows who carried out the research and development of NIPRISAN. In the NIPRISAN case, all the stakeholders mentioned above were adequately involved in the negotiations regarding the licensing of NIPRISAN, except for the researchers and the traditional health practitioner. By any fair assessment, both the researchers and the traditional health practitioner are responsible for the research and development of NIPRISAN, and should be active members of the negotiating team. The non-inclusion of the principal investigator's benefit sharing suggestions constitutes a serious flaw in the License Agreement which arguably violates the principles of equity and fairness enshrined in the CBD.

The SCD trial participants have not benefited from the commercialization of NIPRISAN. In fact, many of them are unable to purchase the medicine due to the relatively current high cost (\$25 per month supply) of NIPRISAN (renamed NICOSAN by XECHEM Inc.). The License Agreement should have made provision to supply NIPRISAN free or at affordable rate (eg \$1.00 per month) to all the SCD trial participants for life. The non-inclusion of specific benefits to trial participants should be avoided in any future licensing agreement of this nature.

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