IRISH MEDICINES BOARD

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HERBAL MEDICINES PROJECT

FINAL REPORT

Monday 14th January 2002

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Executive Summary

The Herbal Medicines Project was established in the Irish Medicines Board following a request by the Minister for Health and Children that the regulation of 'traditional and alternative medicinal products including herbal medicinal products' be reviewed and that a proposal for an interim national licensing scheme be developed [see **Appendix 1**].

The process of developing such a proposal is now complete is and presented here. The development process has involved senior staff of the Irish Medicines Board, an *ad hoc* Scientific Committee on Herbal Medicinal Products established to advise and assist the Irish Medicines Board in this task and extensive consultation with interested organisations throughout Ireland, and the European Union, where appropriate.

In developing this proposal, the Irish Medicines Board and its *ad hoc* Scientific Committee on Herbal Medicinal Products were constantly aware of existing medicines legislation, as well as emerging EU legislation specifically aimed at traditional medicinal products. It is our aim that an interim licensing scheme would be compatible with the pending EU legislation in this area in order to conform to our legal requirements as an EU Member State and to minimise disruption to all parties once EU legislation is introduced.

In addition, a database of traditional and herbal medicinal products was established. This database has provided important information on the potential size of the market that might ultimately fall within the scope of these proposed regulations. A total of 2246 products are now on that database. This number is less than originally anticipated and the total number is expected to increase once regulations are in place.

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PREFACE

Preface

The Irish Medicines Board [IMB] is the Competent Authority responsible for the licensing of the manufacture, preparation, importation, distribution and sale of all medicinal products for human and animal use in Ireland[1]. It is the primary duty of care of the IMB to ensure that public health is protected, as stated in the Irish Medicines Board Act 1995[2].

The need for adequate and appropriate regulation of herbal medicinal products has long been a source of concern to the IMB and its predecessor, the National Drugs Advisory Board [NDAB][3,4].

The growing public demand for these products and the associated increase in their use is evidenced by the large number of shops dedicated to the sale and supply of such products as well as the resurgence of the practice of herbal medicine. It is estimated that by the year 2003 the global expenditure in this area will total 6.6 billion dollars per annum, a figure that reflects an expected annual growth of twenty percent[5].

In response to a request from the Minister for Health and Children in June 2000 [see **Appendix 1**], the IMB initiated the Herbal Medicines Project. The IMB acknowledges that there have been difficulties in the past in licensing herbal medicinal products under standard medicines legislation, particularly in relation to proving clinical efficacy in accordance with existing EU requirements. It should be noted that the EU is also developing new legislation aimed specifically at traditional medicinal products. In light of this, the objective of the project as outlined in the above mentioned request was to develop a proposal for an interim national licensing scheme for 'traditional and alternative medicinal products including herbal medicinal products'. The remit of the project, although broader than herbal medicinal products alone, aimed to reflect the reality of the marketplace and ultimately to appropriately regulate the large number of such unauthorised medicinal products currently available in Ireland.

This document details the final proposals developed over the past eighteen months by the IMB and its *ad hoc* Scientific Committee on Herbal Medicinal Products [SCHMP] in consultation with the key stakeholders in the area [health trade industry, health food stores, consumer groups, medical practitioners, pharmacists and complementary practitioners].

GLOSSARY AND ABREVIATIONS

Glossary

'adverse drug reaction' means a reaction which is harmful and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or treatment of disease or the modification of physiological function[6];

'adverse event' means an undesirable experience occurring following administration of a medicinal product. An adverse event does not necessarily have a causal relationship with the treatment[6];

'advertising' means:

a.) every form of advertising whether in a publication, or by the displaying of any notice, or by means of any letter, press release or other document or by words inscribed in any article, or by the exhibition of a photograph or cinematograph, or by way of sound recording, sound broadcasting or television or in any other way,

b.) any form of door to door information, canvassing activity or inducement designed to promote the supply, sale or consumption of the product and including in particular:

- the advertising to the general public,
- the advertising to health care providers or health food store personnel,
- visits by sales representatives to health care providers or health food store personnel,
- the supply of samples,
- the provision of inducement to sell or supply the product,
- the sponsorship of promotional meetings,
- the sponsorship of scientific congresses[7].

'a medicinal product' is any substance or combination of substances presented for treating or preventing disease in human beings or animals. Any substance or combination of substances which may be administered to human beings or animals

with a view to making a medical diagnosis or to restoring, correcting or modifying physiological function in human beings or animals is likewise considered a medicinal substance[8].

'active ingredient' means the whole herbal/traditional substance[9];

'herbal medicinal product' is any medicinal product, containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations[10];

'herbal preparations' are obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration and fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates[10];

'herbal substances' are all mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually in dried form but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author)[10];

'homoeopathic medicinal product' means any medicinal product prepared from preparations, substances or compounds called homoeopathic stocks in accordance with the homoeopathic manufacturing procedure described in the European Pharmacopoeia or, in the absence of a manufacturing procedure for homoeopathic medicinal products in that pharmacopoeia, in accordance with the homoeopathic manufacturing procedure in any pharmacopoeia in official use in a Member State of the European Community[11];

'immediate packaging' means the container or other form of packaging immediately in contact with the medicinal product[12];

'import' includes procure for importation, and cognate words shall be construed accordingly[13];

'labelling' means information on the immediate or outer packaging[12];

'manufacture' includes:

- total or partial manufacture,
- the various processes of dividing up, packaging or presentation,
- assembly, compounding, filling, formulation, labelling, packaging, processing, and/or
- the importation of a medicinal product from a country other than a Member State of the European Communities[13];

'outer packaging' means the packaging into which is placed the immediate packaging[12];

'package leaflet' means a leaflet containing the information for the user which accompanies the medicinal product[12];

'pharmacist' means a registered pharmaceutical chemist or a registered dispensing chemist and druggist[13];

'prescription', except in the expression medical prescription, means a prescription issued by a registered medical practitioner or a registered dentist[14];

'product authorisation' means an authorisation granted or renewed pursuant to Article 7 of the Medicinal Products (Licensing and Sale) Regulations, 1998 [S.I. No. 142 of 1998][13];

'product registration' means a registration granted pursuant to **Part II** of these regulations.

'qualified practitioner' will be defined as per the proposed Directive on Traditional Medicinal Products[10] when such a definition is available;

'retail sale' means sale to a person buying otherwise than for the purpose of resale[13];

'registered dentist' means a person registered in the register established under the Dentists Act, 1985 [No. 9 of 1985] and includes a person entitled to be so registered by virtue of section 27 (2) (c.) of the said Act[13];

'registered medical practitioner' means a person registered in the register established under the Medical Practitioners Act, 1978 [No. 4 of 1978] and includes any person entitled to be so registered by virtue of section 27 (2) (c.) of the said Act[13];

'registered pharmaceutical chemist' means a person registered in the register of pharmaceutical chemists for Ireland under the Pharmacy Act (Ireland), 1875[13];

'summary of product characteristics' sets out the agreed position of the medicinal product as distilled during the course of the assessment process. It is the definitive statement between the competent authority and the marketing authorisation holder and it is the common basis of communication between the competent authorities of all the Member States. As such the content cannot be changed except with the approval of the originating competent authority.

The SPC is the basis of information for health professionals on how to use the medicinal product safely and effectively. The content of the package leaflet must be consistent with the SPC but in a wording that can be easily understood by non-professionals[15];

'supply' includes sell, distribute or offer or keep for sale or distribution notwithstanding that the person supplied may be in another Member State of the European Community and cognate words shall be construed accordingly[14];

'supply by mail order' means any supply made, after solicitation of custom by the supplier, without the supplier and the consumer being simultaneously present and

using a means of communication at a distance, whether written or electronic, to convey the custom solicitation and the order of supply[14];

'supply by way of wholesale dealing' means the supply of a medicinal product to a person who obtains the product for one or more of the following purposes –

(a.) supply in the course of a pharmaceutical or health trade business, or

(b.) administration in the course of professional practice, or

(c.) for, or in connection with a service provided by a hospital[16];

'the Act' means the *Irish Medicines Board Act, 1995*[2];

'the Board' means the Irish Medicines Board[2];

'the Community' means the European Community as defined in the *Treaty of Rome, 1957*[17], as amended by subsequent Treaties;

'the Minister' means the Minister for Health and Children;

'these regulations' refers to the interim National Licensing Scheme for Traditional Medicinal Products [working title]. NOTE: This document is a proposal, not a regulation.

Abbreviations

ACHM – Advisory Committee on Human Medicines

CHC – Consumers for Health Choice

CMEC – Complementary Medicine Evaluation Committee

CPMP – Committee for Proprietary Medicinal Products

CTD – Common Technical Document

CVMP – Committee for Veterinary Medicinal Products

EC – European Commission

EEA – European Economic Area

EEC – European Economic Community

EHPA – European Herbal Practitioner's Association

EMEA – European Medicines Evaluation Agency

ESCOP – European Scientific Co-Operative on Phytotherapy

EU – European Union

FSAC – Food Safety Advisory Committee

HMPWP – Herbal Medicinal Products Working Party

HMSC – Herbal Medicines Steering Committee

HPA – Health Product Alliance

IAHS – Irish Association of Health Stores

IAMH – Irish Association of Medical Herbalists

ICH – International Conference on Harmonisation

ICGP – Irish College of General Practitioners

IHPA – Irish Herbal Practitioner's Association

IHTA – Irish Health Trade Association

IIAA – Irish and International Aromatherapy Associations

IMB - Irish Medicines Board

IRCHM – Irish Register of Chinese Herbal Medicine

ISH – Irish Society of Homoeopaths

ISPA – International Society of Professional Aromatherapists – Irish Branch

NDAB – National Drugs Advisory Board

NIMH – National Institute of Medical Herbalists

PA – Product Authorisation

Ph. Eur. – European Pharmacopoeia

PIL – Patient Information Leaflet

PRCHM – Professional Register of Chinese Herbal Medicine

PRTCM – Professional Register of Traditional Chinese Medicine

PSI – Pharmaceutical Society of Ireland

PSUR – Periodic Safety Update Report

RCSI – Royal College of Surgeons in Ireland

RDA – Recommended Dietary Allowance

SCHMP – Scientific Committee on Herbal Medicinal Products

SOP – Standard Operating Procedure

SPC – Summary of Product Characteristics

TGA – Therapeutic Goods Administration

WHO – World Health Organisation

INTRODUCTION

Chapter 1 Introduction

1.1 Background

The need for and the difficulties associated with an effective licensing system for herbal medicinal products has been a source of concern for the IMB [formerly the National Drugs Advisory Board – NDAB] for many years. The Medical Preparations (Licensing, Advertisement and Sale) Regulations of 1984[18], which took due account of all relevant European Union [EU] Directives, provided that all medicinal products required a product authorisation in order to be placed on the market in Ireland. According to the regulations cited above, herbal and other traditional products with acknowledged medicinal properties or, which made a claim to such properties, were classified as medicines.

In August 1985 the NDAB published 'Guidelines for Application for Product Authorisation of Herbal Products'[4]. This document attempted to address the difficulties associated with the regulation of herbal medicinal products under Council Directive 65/65/EEC[8] as implemented in Ireland, most notably in relation to the requirements for proof of quality, safety and efficacy. Despite efforts to assess herbal medicinal product applications in accordance with the above legislation, a large number of products could not be authorised due particularly to insufficient data relating to efficacy and safety and consequently their legal status has been a continuing source of concern.

In 1993 the Food Safety Advisory Committee [FSAC] prepared a document entitled 'Food Supplements and Health Foods' for the Department of Health and the Department of Agriculture, Food and Forestry[19]. This document clearly states that natural materials whose composition and status have not been established should be subject to approval by the regulatory authority in order to establish quality and safety, prior to importation and/or prior to marketing. The report also recommends that herbal teas should not contain toxic plants and should not, either directly or indirectly, make any medicinal claim. This report also suggests that the materials used in herbal teas and essential oils be required to meet recognised safety standards.

In 1999, in view of the increasing use and availability of herbal medicinal products, especially those without authorisation, the IMB published the 'Guide to the Definition of a Medicinal Product[20]' which confirmed that herbal medicinal products, according to the definition outlined in Council Directive 65/65/EEC[8], continue to be classed as medicinal products and must therefore be regulated as such. This guideline simply re-stated the position in the context of the existing legislation.

In the same year, following a review of all relevant information, the IMB communicated to the Department of Health and Children its recommendation that products containing St. John's Wort [*Hypericum perforatum*] should only be available on medical prescription. This recommendation was made on the basis that products containing this herbal substance were promoted for the treatment of depression, an indication itself requiring some control [Medical Preparations (Advertising) Regulations, 1993[7], as amended] and generally considered to be unsuitable for self-diagnosis and self-medication. The information examined by the IMB clearly demonstrated the potential of this herbal substance as an antidepressant. In addition to the therapeutic indication claim, there were a number of safety concerns relating to the inherent toxicity of the herbal substance itself and its interactions with orthodox medicines [cyclosporin[21], the oral contraceptive pill[21], warfarin[21], theophylline[22]]. Following this recommendation by the IMB, the Department of Health and Children confined St. John's Wort to prescription control [Medicinal Products (Prescription and Control of Supply) (Amendment) Regulations, 1999[23]] from 1st January 2000.

In December 1999, a Dáil statement by the Minister for Health and Children highlighted the need for a specific interim national system for the licensing of certain herbal and/or traditional medicinal products. In January 2000, the IMB made representation to the Department of Health and Children outlining a proposal to move forward the issue of control of herbal medicines in Ireland. Following a meeting with the Minister and in order to review the possible requirements of an effective regulatory system for herbal medicinal products, an internal IMB Herbal Medicines Steering Committee [HMSC] was established consisting of Dr. Frank Hallinan [Chief Executive], Dr. J. Michael Morris [Pharmaceutical Director], Dr. Joan Gilvarry [Acting Medical Director], Dr. Elaine Breslin [Senior Medical Officer], Ms. Christl Kloos [Senior Pharmaceutical Assessor] and Ms. Rita Purcell [Director of Finance

and Administration]. This HMSC highlighted the need for a specific project to deal with herbal medicines and the additional staff required by the IMB to run such a project. The Herbal Medicines Project was then firmly established with the appointment of a full-time Herbal Medicines Project Manager. Dr. Dairine Dempsey took up this position on 4th September 2000.

1.2 Preliminary Consultation

In order to ensure that the Herbal Medicines Project was both open and transparent to all interested parties and the general public the following steps were taken:

1.2.1 Advertisement in the National Press/on the IMB web site

On 29th September 2000 an advertisement was placed in three national newspapers [The Irish Times, The Irish Independent and The Irish Examiner] and on the IMB web site requesting public comment on all aspects of a possible interim national licensing scheme for traditional, alternative and/or herbal medicinal products [see **Appendix 2**]. The advertisement outlined the aim of the new scheme as described by the Minister in his letter dated 23rd June 2000 [see **Appendix 1**] and detailed briefly the issues which the IMB considered most important in the development of a new scheme. Responses were requested within one month i.e. on or before 5pm on the 31st October 2000. By the closing date, 31 responses had been submitted. Over the following weeks the final number of submissions reached 41 [see **Appendix 3**], all of which were accepted and reviewed.

Of these, 12 submissions dealt, in varying degrees of detail, with the three main issues i.e. the Scope, the Development Process and the New System. Of the remaining 29, six failed to address any of the issues raised in the advertisement, eight addressed just one of the three main topics and 13 submissions addressed two of three issues.

Further evaluation of the responses showed that 20 of the 41 responses were from interested members of the general public or individual members of interested organisations, seven were from pharmaceutical or other interested manufacturers, one submission was received from a school of alternative medicine and two from miscellaneous groups. The remaining 11 submissions from 12 interested

organisations [see **Table 1**] were from those organisations known to the IMB [marked in bold in **Table 1** and discussed further in **Chapter 1.2.2**] and others.

Table 1 Interested organisations and their representatives

Organisation	Representative
International Society of Professional Aromatherapists [ISPA]	Geraldine Lavelle
Irish Health trade Association [IHTA]	Martin Murray
Consumers for Health Choice [CHC]	Breda Dooley
Irish Association of Medical Herbalists [IAMH]	Dympna Kennan
Irish Herbal Practitioner's Association [IHPA]	Helen McCormack
National Institute of Medical Herbalists [NIMH] *	Alison Denham
Irish and International Aromatherapy Associations [IIAA]	Nicola Darrell
Professional Register of Traditional Chinese Medicine [PRTCM] **	Mary Plunkett
Professional Register of Chinese Herbal Medicine [PRCHM] **	Kerry McBride
European Herbal Practitioner's Association [EHPA] *	Michael McIntyre
Irish Association of Health Stores [IAHS]	Brod Kearon
Irish Society of Homoeopaths [ISH]	Sally Quinlan

*UK or European based organisations; ** Joint submission

1.2.2 Consultation with Interested Organisations

In addition to the public notice, the IMB also formally contacted those organisations known to the IMB to have an interest in herbal medicines. A letter and a copy of the advertisement was sent out to the following organisations on the 28th September 2000:

- Consumers for Health Choice [CHC]
- Health Products Alliance [HPA]
- Irish Association of Health Stores [IAHS]
- Irish Association of Medical Herbalists [IAMH]
- Irish Health Trade Association [IHTA]
- Irish Register of Chinese Herbal Medicine [IRCHM]

In addition to the above groups, the Professional Register of Traditional Chinese Medicine [PRTCM] contacted the IMB to express their interest. This group were then formally invited to make a submission.

The HPA informed the IMB that it was an umbrella body representing the IAMH, the IAHS and the IHTA and that it was beyond its remit to comment on the regulation of herbal medicinal products as it was established to deal solely with the issue of St. John's Wort. Following initial written consultation, the IAMH and the IRCHM also

formed an umbrella organisation, the Irish Herbal Practitioner's Association [IHPA], who responded on behalf of both groups. The IAMH also submitted a separate response on their own behalf. Each of the remaining groups contacted also took the opportunity to make their position known to the IMB. The associations and the umbrella groups to which they belong are detailed in **Appendix 4**.

1.3 Establishment of an *ad hoc* Scientific Committee on Herbal Medicinal Products

Following initial consultation with the general public and interested organisations, an *ad hoc* Scientific Committee on Herbal Medicinal Products [SCHMP] was established. This committee is a panel of scientific experts having a special knowledge in herbal medicine and/or related areas and whose role is to advise and assist the IMB in matters pertaining to the development of an interim national licensing scheme [see **Appendix 5** – Terms of Reference].

Dr. Desmond Corrigan, Director of the School of Pharmacy, Trinity College, Dublin, was nominated by a member of the public to serve on the *ad hoc* SCHMP and also proposed by the IMB. Dr. Corrigan is an acknowledged international expert in herbal medicine/pharmacognosy and has been involved in this area at a European level for more than ten years. On this basis, the IMB invited Dr. Corrigan to be chairperson of the *ad hoc* SCHMP.

It was the intention that the *ad hoc* SCHMP be established as a group of experts and not as a group representing interested parties. In the interest of fairness and as part of the consultation processes outlined in **Chapter 1.2**, the public and interested parties were asked to put forward nominations for membership of the *ad hoc* SCHMP. Most parties agreed that the establishment of such a committee was important for the success the project and a total of 15 names were proposed as part of the consultation process. In addition, the IMB nominated eight candidates for consideration by the chairperson for membership of the proposed committee. Dr. Corrigan, the chairperson of the *ad hoc* SCHMP suggested one additional nominee.

From the suggestions received the chairperson selected those people whom he deemed appropriate and who were available to join the committee. The members were chosen with a view to establishing a balanced committee consisting of people from a variety of backgrounds who would effectively reflect and represent the many views and opinions on herbal medicines and herbal medicines regulation. Appointed members were required to sign a confidentiality agreement and to declare any conflicts of interest [see **Appendix 6**]. The final membership of the *ad hoc* SCHMP is detailed in **Table 2**.

Table 2 Members of the *ad hoc* Scientific Committee on Herbal Medicinal Products

Member	Discipline	Role on the Committee
Mrs. Ingrid Hook	Pharmacognosy	Scientific Advisor
Dr. Helen Sheridan	Phytochemistry	Scientific Advisor
Professor Edzard Ernst	Complementary Medicine	Scientific/External Advisor
Dr. Katherine Chan Mullen	General and Chinese Medicine	Medical Advisor
Dr. Dilis Clare	General and Herbal Medicine	Medical/Herbal Advisor
Ms. Helen McCormack	Herbal Medicine	Herbal Advisor
Ms. Nicola Darrell	Herbal Medicine	Herbal Advisor
Ms. Geraldine Lavelle	Pharmacy and Aromatherapy	Pharmacy/Aromatherapy Advisor

The first meeting of the *ad hoc* SCHMP took place on 15th December 2000. The Committee met on six other occasions:

- 31st January 2001
- 23rd March 2001
- 16th May 2001
- 25th June 2001
- 31st July 2001
- 24th September 2001

As and when potential chapters of this report were agreed by the IMB and the *ad hoc* SCHMP, they were released for comment to the Department of Health and Children and interested organisations [see **Chapter 1.4**].

1.4 Transparency and Open Consultation

The following process of consultation was adopted by the IMB, the *ad hoc* SCHMP and the Department of Health and Children:

- The IMB/SCHMP agreed individual chapters of the final report at each SCHMP meeting,
- Agreed chapters were sent to the Department of Health and Children with two weeks for comment,
- Where issues were raised these were discussed by the IMB/SCHMP
- Where no issues were raised, the chapters were sent to interested organisations with a period of two weeks for comment,
- In as far as is possible, suggestions and comments were taken on board by the IMB/SCHMP,
- The final draft document was considered by the IMB Expert Sub-Committee of the Advisory Committee on Human Medicines, the Advisory Committee on Human Medicines [ACHM] and the Board,
- Once endorsed the draft report was placed on the IMB web site for one month for public comment.

Following the above consultation process the final report will be sent to the Department of Health and Children for consideration. This process of consultation aimed to give interested organisations an opportunity to comment on the outcome of the deliberations of the IMB and the *ad hoc* SCHMP on an on-going basis. The chairperson of each interested organisation that agreed to partake in the process was required to sign a confidentiality agreement before consultation [see **Appendix 7**]:

- College of Anaesthetists of the Royal College of Surgeons of Ireland [RCSI]
- Consumers for Health Choice [CHC],
- European Herbal Practitioner's Association [EHPA]
- International Society of Professional Aromatherapists – Irish Branch [ISPA],
- Irish and International Aromatherapy Associations [IIAA],
- Irish Association of Health Stores [IAHS],
- Irish Association of Medical Herbalists [IAMH],
- Irish College of General Practitioners [ICGP],
- Irish Health Trade Association [IHTA],
- Irish Herbal Practitioner's Association [IHPA],
- Irish Register of Chinese Herbal Medicine [IRCHM],
- National Institute of Medical Herbalists [NIMH],

- Pharmaceutical Society of Ireland [PSI].

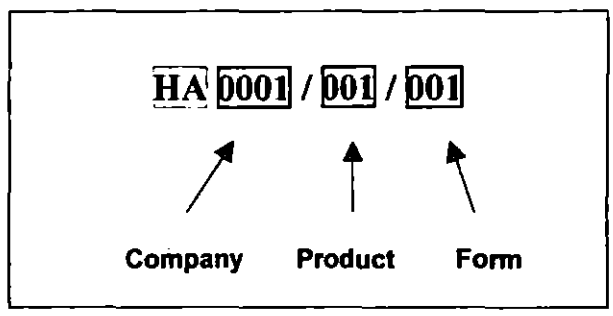
The Professional Register of Traditional Chinese Medicine declined to take part in the process.

Consultation took the form of four consultation documents, which outlined the details of those chapters agreed by the IMB and the *ad hoc* SCHMP on an on-going basis. On each occasion, the CHC, the EHPA, the IAHS, the ICGP, the IHTA, the IRCHM, and the NIMH submitted comments. Comments were submitted by the IAMH and the PSI on two of the four consultation documents. Comments were reviewed by both the IMB and the *ad hoc* SCHMP. A letter of response was sent to each organisation following this review and, where deemed appropriate, suggestions were incorporated into this proposal.

1.5 Traditional Medicinal Products Database

A decision was taken to determine the number of products on the market in Ireland that might ultimately be regulated under the proposed interim national licensing scheme. The IHTA and the IAHS were contacted and, following a meeting with the IMB, a template for the product information required was agreed [see **Appendix 8**].

The details of a total of approximately 2000 products were submitted to the IMB for inclusion on the proposed database. These products have been up loaded onto the IMB Swedis product database and assigned HA numbers using the established product authorisation [PA] format:



Of the 2003 products, 1909 are considered herbal, 60 are considered traditional and the remaining 34 are combination products. These figures indicate that the information on a large number of traditional medicinal products, as defined in these

regulations [see **Chapter 3**, Article 2], and combination type products has not yet been submitted to the IMB. Once regulations are put in place it is proposed that a strict timeline for submission of traditional medicinal product registration applications be imposed on all persons responsible for marketing such products in Ireland in order to ensure that all products that fall within the scope of the proposed regulations are made known to the Competent Authority [see **Chapter 3**, Article 16].

In addition, a number of products currently on the IMB PA database could also come under the scope of the proposed regulations. Of the 243 products in question, 195 are considered herbal, 41 are traditional and 7 are combination products. Only nine of these products currently hold full marketing authorisations. Of the remaining 234, two have been rejected, three have been cancelled, 34 were withdrawn by the applicant and 179 applications are currently under consideration by the IMB for authorisation under standard medicines legislation. Given the difficulties encountered in the past in licensing traditional medicinal products under standard medicines legislation, particularly in relation to proving clinical efficacy, it is likely that many of these products would be better served under the proposed new interim national licensing scheme for traditional medicinal products.

Finally it should be noted that the details of approximately 400 additional products from three individual companies have been requested but have not yet been submitted.

PROPOSED EU DIRECTIVE ON TRADITIONAL MEDICINAL PRODUCTS

Chapter 2 Proposed EU Directive on Traditional Medicinal Products

2.1 Background

Following acknowledgement by the European Commission that traditional medicinal products are not adequately accommodated for by Council Directive 65/65/EEC[8], the European Commission [EC] Pharmaceutical Committee released the first draft of a proposal for a Directive on a registration procedure for traditional medicinal products [Provisions of a Directive on Traditional Medicinal Products[24]] in November 2000. Details of the internal IMB Herbal Medicines Steering Committee comments on this draft can be seen in **Appendix 9**. Our understanding was that the proposed Directive was under development in order to legislate for a large section of the EU medicines market currently unregulated. The original proposal as per 'Provisions of a Directive on Traditional Medicinal Products[24]' outlined a brief not dissimilar to that of the IMB Herbal Medicines Project at national level.

In April 2001, the second draft [Directive on Traditional Medicinal Products – Draft No. 2[25]] was circulated for comment. The Irish comments represented the views of the HMSC and the IMB's newly established *ad hoc* SCHMP [see **Appendix 10**].

The broad scope of the original drafts was welcomed by the IMB. However, reservations were expressed with regard to the proposal that in order for a product to be registered under this Directive, the product in question or a 'corresponding product' must have 'been in use in one or more Member States throughout a period of 30 years immediately preceding the date of the application'[24]. It is our opinion that this provision, as an inclusion/exclusion criterion, does not reflect the nature of traditionally used medicinal products. This requirement is reduced to 15 years where evidence can be provided of 30 years continuous usage in either (i) a specified territory or territories outside the EU or (ii) partly in one or more Member States and partly in such a specified territory or territories. It is the opinion of the IMB/SCHMP that this provision may discriminate against those products that originate in non-EU

traditions e.g. Chinese Herbal Medicinal Products, Ayurvedic [Indian] Medicinal Products etc.

In June 2001 the latest draft of the proposed Directive [Directive on Traditional Herbal Medicinal Products[10]] was obtained by the IMB. This version is significantly different to previous drafts and maintains both the '30 year rule' and the '15 year rule for non-EU products'. In addition this draft proposes to narrow the scope to cover 'traditional herbal medicinal products' only. The IMB/SCHMP acknowledge that the remit of the Herbal Medicines Project, as outlined by the Minister for Health and Children [see **Appendix 1**], is broader than that of the proposed Directive.

2.2 Future

It is expected that this latest draft of the proposed Directive[10] will not be officially circulated to the Member States for comment at this stage. It is our understanding that it will now go to the Council of Ministers and then the European Parliament. Opportunity to comment further will therefore be at a political rather than a scientific level.

PROPOSED NATIONAL REGULATORY FRAMEWORK

Chapter 3 Proposed National Regulatory Framework

3.1 Introduction

The *ad hoc* SCHMP and the IMB put forward the following proposal for an interim national licensing scheme for the regulation of 'traditional and alternative medicinal products including herbal medicinal products' as requested by the Minister for Health and Children [see **Appendix 1**].

It should be noted that during the course of the development process the IMB and the *ad hoc* SCHMP reviewed and considered a number of potential systems of regulation for traditional medicinal products with reference to those systems operational in other EU, as well as in non-EU countries. The Canadian approach, whereby all 'Natural Health Products' are regulated by an agency independent of both the medicines and the food agencies in Canada, was reviewed in some detail. The IMB/SCHMP considered that they could not recommend such a system in the Irish context, where the IMB is the Competent Authority in Ireland with responsibility for all medicines. In addition, concern was expressed with regard to the potential cost to the health trade industry, and ultimately to the consumer, of establishing an independent regulatory body for traditional medicinal products. Such a body would require facilities and staff to cover traditional medicinal product assessment [ultimately both human and veterinary], inspection of manufacture and wholesale sites, pharmacovigilance and enforcement, as well as the associated administrative costs. Finally, as a Member State of the EU, it would not be possible for Ireland to regulate traditional medicines and food supplements as 'Natural Health Products', as these are regulated separately in accordance with EU law.

Throughout the development process, the IMB and the *ad hoc* SCHMP were also mindful of parallel developments at EU level with the emergence of an EU Directive on Traditional Herbal Medicinal Products[10], as outlined in **Chapter 2**. In order to minimise disruption for consumers and industry it is our goal to ensure that the new national scheme will include all provisions as per the proposed EU Directive. However, the IMB accepts that the scope of the proposed interim national scheme, as

outlined by the Minister for Health and Children [see **Appendix 1**], is broader than that outlined in the latest draft of the proposed Directive[10].

3.2 Preamble

The IMB and the *ad hoc* SCHMP would like to take this opportunity to highlight a number of issues that emerged during the process of developing this proposal which were central to the outcome of the work.

3.2.1 The Remit of the Herbal Medicines Project

The remit of the Herbal Medicines Project as outlined by the Minister in his letter to the IMB of the 23rd June 2000 [see **Appendix 1**] is as follows:

'to advise the Minister in relation to a scheme that might be introduced in this country in respect of the licensing of 'traditional and alternative medicinal products, including herbal medicinal products'

and any such recommendation should:

(a) adequately define the medicinal products to which it relates;

(b) adequately address the standards of quality and safety, and

(c) where the standard proof of efficacy has not been met, the products concerned should –

(i) be appropriately identifiable,

(ii) where medicinal claims are made, be such that any such claims in respect of the use of such a product are appropriate having regard to the fact that the standard proof of efficacy has not been met; and

(iii) be otherwise such that the interests of public health are adequately protected.

The Department of Health and Children acknowledged at that time that such a licensing system would be provided for by means of regulations. To this end the following chapter is a proposed regulatory framework for such a scheme.

3.2.2 The Limitations of Existing and Pending EU Legislation

The IMB and its *ad hoc* SCHMP undertook to develop a proposal for an interim national licensing scheme that was, in as far as was possible, compatible with the existing medicines legislation i.e. Council Directive 65/65/EEC[8] and associated legislation and the proposed EU Directive on Traditional Herbal Medicinal Product[10]. The former legislation was adopted by Ireland upon entering the EEC in 1973. It should be pointed out that a number of submissions received as part of the consultation process outlined in **Chapter 1.4** were critical of this legislation, particularly in relation to its applicability to traditional medicinal products. However, as a Member State of the European Union and the Competent Authority responsible for medicines in Ireland, the IMB and its *ad hoc* SCHMP agreed that it was most appropriate to work within existing medicines legislation. It is acknowledged that amendment of such legislation is outside the remit of the Herbal Medicines Project.

In accordance with Council Directive 65/65/EEC[8], it was noted that a medicinal product is defined as follows:

'any substance or combination of substances presented for treating or preventing disease in human beings or animals'

'any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings or in animals is likewise considered a medicinal product'

where a substance is defined as *'any matter irrespective or origin which may be: - human, animal, **vegetable**, or chemical'*.

In addition, the EU is preparing a Directive on Traditional Herbal Medicinal Products[10]. This Directive, as outlined in **Chapter 2**, is expected to become law as early as 2002. The IMB and the *ad hoc* SCHMP were mindful of these developments at European level and have incorporated many of the provisions of the proposed Directive[10] into the interim national licensing scheme.

It should be pointed out however, that a number of the proposals in the draft Directive[10] have been incorporated into this proposal despite the reservations that exist among members of the IMB and the *ad hoc* SCHMP as to their suitability. These are discussed in more detail below:

3.2.2.1 Definition of 'Traditional Medicinal Product'

The draft Directive on Traditional Herbal Medicinal Products[10] makes no attempt to define the term 'Traditional Medicinal Product', other than to stipulate that such a product *'or a corresponding medicinal product has been in medicinal use in the Community throughout a period of at least 30 years preceding the date of application'*. It is the opinion of the IMB and the *ad hoc* SCHMP that this does not adequately or accurately reflect the essential nature of the concept of a traditional medicinal product. This '30 year rule' fails to accommodate many traditional medicinal products that, for one reason or another, cannot provide evidence of continuous medicinal use in Ireland or in another EU Member State for 30 years.

A number of possible alternatives to the above were discussed by the IMB and its *ad hoc* SCHMP including an option to define 'traditional medicinal product' and specify this as an inclusion criterion, for example:

'A traditional medicinal product is a medicinal product containing as active ingredients, generally herbal substances, herbal preparations but also other non-herbal substances, that are supplied on the basis of their use in an established tradition of practice'.

The IMB/SCHMP also noted the definition adopted by the Complementary Medicines Evaluation Committee [CMEC] of the Australian national regulatory authority, the Therapeutic Goods Administration [TGA], relating to traditional use:

'Traditional use refers to documentary evidence that a substance has been used over three or more generations of recorded use for a specific health related or medicinal purpose.

In forming a claim based on traditional use, products and substances which form part of the traditional therapies should identify the therapy to which they belong, or the paradigm in which the therapy has been traditionally used, as well as the product description/name and the symptom/indication/condition for which the product or substance is claimed to be beneficial.[26]'

This definition acknowledges the theories, concepts and cultural context of the therapy when considering the proposed 'traditional use' claim.

The IMB/SCHMP noted that the latest draft of the Canadian Natural Health Products Proposed Regulatory Framework[27] defines a Natural Health Product as follows:

Products manufactured, sold or represented for use in

(i) the diagnosis, treatment, mitigation or prevention of a disease, or abnormal physical state or its symptoms in humans;

(ii) restoring or correcting organic functions in humans, or

(iii) maintaining or promoting health or otherwise modifying organic functions in humans.

This is similar to the definition of a medicinal product as per EU Council Directive 65/65/EEC[8] and although this definition is designed to include 'a substance or substances used as a traditional medicine', it does not attempt to define what a 'traditional medicine' is.

3.2.2.2 Traditional Medicinal Products from Other Ethnic Traditions

In addition to the proposed '30 year rule' outlined above and in accordance with the draft EU Directive on Traditional Herbal Medicinal Products[10], products that have been available outside the EU for 30 years ['in a specified territory'] must provide additional evidence of availability in an EU Member State for 15 years.

It is the opinion of the IMB and the *ad hoc* SCHMP that this provision might restrict the number of products from traditions other than the western European tradition that would otherwise be eligible for registration under the proposed Directive[10] and by extension under the interim national licensing scheme.

3.2.2.3 Overall Comment

Ideally the IMB and its *ad hoc* Scientific Committee on Herbal Medicinal Products would favour a change in the proposed Directive to allow a more open interpretation of the concept of 'traditional use' as indicated in our responses to the first and second drafts of the Directive [see **Appendices 9-10**]. At a minimum the word 'throughout' should be removed from the proposed definition of 'traditional use', as this appears to imply a requirement to prove continuous use in the EU over the requisite 30 years. The provision of Article 4.3 c) of the proposed Directive[10] would then read as follows:

*'bibliographical or expert evidence to the effect that the medicinal product in question, or a corresponding medicinal product has been in medicinal use in the Community ~~throughout a~~ **for a** period of at least 30 years preceding the date of application. The requirement to show medicinal use ~~throughout~~ **during** this period is satisfied even where the marketing of the product has not been based on a specific authorisation. It is likewise satisfied if the number or quantity of ingredients of the medicinal product has been reduced during the period as mentioned in this article.*

A corresponding medicinal products is characterised by

i) same active ingredients, irrespective of excipients used;

ii) same or similar intended purpose;

iii) equivalent strength;

iv) same or similar route of administration

as the medicinal product applied for.

Overall the IMB/SCHMP acknowledge that in order to comply with and allow ease of transition to the pending EU legislation, the following proposal for an interim national licensing scheme should incorporate the same inclusion criteria as the proposed EU Directive[10]. It is the opinion of the IMB and its *ad hoc* SCHMP that by adopting the provisions as proposed at EU level, any disruption to consumers and industry will be reduced. However, the IMB and its *ad hoc* SCHMP would support and will continue to suggest, where appropriate, that the proposed Directive[10] adopt a more flexible and inclusive approach.

3.2.3 Registration of Non-Medical Practitioners

The IMB and the *ad hoc* SCHMP acknowledge that the registration of non-medical practitioners is outside the remit of the Herbal Medicines Project. However, it is considered necessary to highlight the fact that the following proposals will fall short of effectively regulating the traditional medicines market in the absence of a provision for non-medical practitioners to have legitimate access to traditional medicinal products, herbal substances and herbal preparations for the treatment of patients under their care.

In relation to medical herbalists, it is our understanding that extemporaneous preparation of complex mixtures of herbal substances and/or preparations is central to the practice of medical herbalism. Statutory self-regulation of this professional group would better safeguard public health by ensuring that practitioners, for whom exemptions from these regulations are proposed, have appropriate training. The IMB/SCHMP believe that an interim national licensing scheme should not require that herbal practitioners obtain a Manufacturer's Licence and/or a product registration/authorisation for herbal preparations extemporaneously compounded by them for individuals under their care.

The Irish Herbal Practitioners Association has presented the following proposal for an interim provision for such exemptions to the Department of Health and Children:

Exemption in respect of herbal remedies:

12.(1) The restrictions imposed by sections 7 and 8 of this Act do not apply to the sale, supply, manufacture or assembly of any herbal remedy in the course of a business where –

a) the remedy is manufactured or assembled on premises of which the person carrying on the business is the occupier and which he is able to close so as to exclude the public, and

b) *the person carrying on the business sells or supplies the remedy for administration to a particular person after being requested by or on behalf of that person and in that person's presence to use his own judgement as to the treatment required.'*

It should be noted that the reference to 'sections 7 and 8 of this Act' above refers to the United Kingdom Medicines Act 1968[28] from which the text of this exemption is originally taken.

3.3 Part I Definitions and Scope

The term 'alternative medicinal product' as per the original remit of the Herbal Medicines Project outlined by the Minister for Health and Children [see **Appendix 1**] was considered imprecise. It is proposed to omit this term from these regulations.

All traditional herbal and traditional non-herbal medicinal products available on the market in Ireland shall be subject to registration to be co-ordinated by the Competent Authority for traditional medicinal products in Ireland.

EXPLANATORY NOTE

Part 1 of these regulations is designed to clearly define those medicinal products that fall within the scope of the proposed interim licensing scheme.

Article 1 Scope of Application

1. These regulations apply to traditional herbal medicinal products for human use.

2. These regulations apply to the following traditional non-herbal substances when used in medicinal products or where medicinal claims are made or inferred:
    - fish oils,
    - royal jelly and other insect products,
    - activated charcoal and other therapeutic clays.
    - acidophilus/acidobifidus/lactobacillus and other bacterial products,
    - other.

3. These regulations apply to combinations of traditional herbal substances or to combinations of traditional non-herbal substances [Articles 1.2-1.3] and/or preparations thereof with other non-herbal, non-traditional substances [e.g. vitamins/minerals below levels at which they are considered to fall within standard medicines legislation], where the primary active ingredient of such a product is the traditional herbal or traditional non-herbal substances/preparations.

EXPLANATORY NOTE TO ARTICLE 1

Article 1 provides that all herbal medicinal products that have a use based on a recognised tradition of practice, including those from non-Western traditions, are within the scope of this regulation.

Other non-herbal substances that fall within the scope of this regulation are listed in Article 1.2.

The substances listed in Article 1.3 are those that fall within the scope of these regulations when they are presented, advertised or labelled to indicate a medicinal use. This list is not exhaustive and the final provision of 'other' ensures that any traditional non-herbal substance that is not specifically listed but that makes a medicinal claim is covered by these regulations.

Article 1.4 provides that any medicinal product containing as the principle active ingredient a traditional herbal substance and/or a traditional non-herbal substance is considered to fall within the scope of these regulations even where the product also contains other ingredients, provided they are not covered by other legislation that takes precedence.

Article 2 Definitions

Traditional is defined as having been 'in medicinal use in the Community throughout period of at least 30 years preceding the date of application. The requirement to show medicinal use throughout this period is satisfied even where the marketing of the product has not been based on a specific authorisation. It is likewise satisfied if the number or quantity of ingredients of the medicinal product has been reduced during the period as mentioned in this article.

As an alternative to supplying evidence of medicinal use throughout a period of 30 years within the EU, the applicant may supply evidence of medicinal use throughout a period of 30 years in either:

(i) a specified territory or territories outside the Community, or

(ii) partly in one or more Member State and partly in such a specified territory or territories,

if during this period the product has been available within the Community for at least 15 years.

2. **Herbal Medicinal Product** is any medicinal product, containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations.

3. **Herbal Substances** are all mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually in dried form but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system [genus, species, variety and author].

4. **Herbal Preparations** are obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration and fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates.

5. A **Non-Herbal Medicinal Product** is any medicinal product containing as active ingredient(s) one or more of those substances listed in Article 1.2 and, where applicable, Article 1.3.

EXPLANATORY NOTE TO ARTICLE 2

The definition of 'traditional' in Article 2.1 is consistent with the requirements outlined in the pending European legislation[10] in this area. It is acknowledged that this may not be the most desirable description of the term 'traditional' but is one that must be adopted to ensure conformity with EU law and to avoid disruptive legal challenges to the validity of the proposed interim national scheme [see **Chapter 3.1.2**].

The second part of Article 2.1 is designed to allow traditional medicinal products from other ethnic traditions such as Traditional Chinese Medicine, Ayurvedic Medicine, Tibetan Medicine, and Kampo [Japanese] Medicine to be registered in Ireland. Once again the use of a timeframe to define tradition may not be ideal but is considered appropriate in view of the proposed Directive[10] [see **Chapter 3.1.2**].

Definitions 2.2 – 2.4 are in line with the proposed EU definitions[10] and are therefore incorporated into these regulations.

It should be highlighted that, in accordance with Article 2.3, all marine-based products are considered to fall within the scope of these regulations. In addition, the definition outlined in Article 2.4 includes herbal teas and herbal juices. It is acknowledged that many herbal teas/juices may be considered food products and as such decisions on these products will be made on a case-by-case basis. This provision is designed to ensure that all traditional/herbal medicinal products available in Ireland will be required to be registered with the Competent Authority prior to being placed on market.

The complex issue of herbal extracts was discussed in some detail by the IMB/SCHMP. It is clear from the definition provided in Article 2.4 that these products are within the scope of these regulations. However, it was noted that this area is currently the subject of a review by the European Pharmacopoeia. It was agreed that we should await the outcome of this review before a definitive statement on the specific inclusion/exclusion of the different types of extracts is defined.

The IMB/SCHMP agreed that *Aloe vera* and essential oils products for external use should only be subject to registration where medicinal claims are made or inferred either directly on the product or in associated advertising/literature.

The final section of this Article covers traditional substances other than traditional herbal substances that will be covered by these regulations.

Article 3 Exemptions from Product Registration

1. These regulations do not apply to any herbal or non-herbal medicinal product that should be authorised according to the Medicinal Products (Prescription and Control of Supply) Regulations, 1996[14] as amended and/or the Medicinal Products (Licensing and Sale) Regulations, 1998[13] as amended. Products covered by the Misuse of Drugs Act, 1977[29] and/or the Poisons Act, 1961[30] as amended, are likewise excluded from these regulations.

2. These regulations do not apply to products containing one or more vitamin substances or one or more mineral substances or one or more such vitamin substances in combination with one or more such mineral substances.

3. These regulations do not apply to homoeopathic medicinal products as defined by Council Directive 92/73/EEC[11]. Pending the on-going review of Council Directive 92/73/EEC[11], it is proposed that Bach and other flower remedies, as well as anthroposophic medicinal products, will likewise be excluded.

EXPLANATORY NOTE TO ARTICLE 3

Article 3 details those substances and products that will not be covered by these regulations. Traditional medicinal products that require prescription control either by virtue of their intended use or concerns regarding their safety will not be covered by these regulations. Such products will require product authorisation as per Council Directive 65/65/EEC[8] and associated legislation. By definition, medicinal products that require prescription control cannot be sold over-the-counter. In the interest of public safety, the supply of such products only follows a full consultation with a medical practitioner.

Vitamin and mineral products are outside the scope of these regulations. These products are currently regulated in accordance with Food Law when the levels of vitamins and minerals are below the Recommended Dietary Allowance [RDA]. Products containing vitamins and minerals in excess of the RDA are medicines and must be authorised in accordance with Medicinal Products (Licensing and Sale) Regulations, 1998[13].

Homoeopathic medicinal products are regulated according to Council Directive 92/73/EEC[11]. This Directive is currently under review and it is anticipated that flower remedies and anthroposophic medicinal products will be considered for possible inclusion within the scope.

3.4 Part II Product Registration

A product registration will be issued by the Competent Authority following receipt and assessment of a product registration application in accordance with these regulations.

EXPLANATORY NOTE

Part II of these regulations specifies the types of medicinal products that will be eligible for registration under this scheme. In addition, this section details the information to be provided by the applicant as part of an application for a product registration under these regulations.

Article 4 Criteria for Product Registration

In order to qualify for registration in accordance with these regulations, a medicinal products must:

(i) Comply with Article 2.1, and

(ii) Comply with Article 2.2 or Article 2.5.

EXPLANATORY NOTE TO ARTICLE 4

In accordance with Article 4 products that can be registered under these regulations are limited to those comprising herbal substances, herbal preparations or non-herbal substances [as per Article 2] that have a medicinal use based on an established tradition of practice. For the purposes of these regulations, tradition is defined as having been in medicinal use for at least 30 years in the EU prior to the date of application or, at least 15 years within the EU where use outside the EU for 30 can be proven.

Article 5 Application for Product Registration

1. In order to obtain product registration, the applicant must submit an application to the Competent Authority for traditional medicinal products in Ireland.

2. The applicant must hold a valid Manufacturer's or Wholesaler's Licence from the Irish Competent Authority or the Competent Authority of another Member State – see Articles 20-21.

3. Each registration application submitted should include the following:

   (i) administrative details [product name, composition, manufacturer etc.]
   (ii) summary of product characteristics [SPC] – see Article 6,
   (iii) details of any authorisation or registration, obtained by the applicant in another EU Member State or third country, to place the medicinal product on the market, and details of any decision to refuse to grant or to suspend or revoke an authorisation or registration and the reasons for such a decision,
   (iv) evidence that the person seeking to register the product holds a valid Manufacturer's or Wholesaler's Licence as per Articles 20-21,
   (v) copies of proposed product label and patient information leaflet,
   (vi) bibliographic evidence to the effect that the medicinal product in question or a corresponding medicinal product has been in medicinal use in the EU throughout a period of at least 30 years preceding the date of application [see Article 2.1],
   (vii) a full quality dossier – see **Part III**,
   (viii) a bibliographic review of the safety data. For combination products, such data should relate to the specific combination; the data need to relate to individual active ingredients only, if they are not sufficiently known [cf. Article 4.3a) - proposed EU Directive[10]] – see **Part IV**,
   (ix) evidence in support of the traditional status of the product and the proposed traditional use claim – see **Part V**,
   (x) an expert report that details, explains, justifies and validates the information submitted under (vi) - (ix) above.

EXPLANATORY NOTE TO ARTICLE 5

Each application submitted to the Competent Authority under these regulations should include the above documentation.

The specific requirements for the SPC, the quality dossier, evidence of safety and evidence of the traditional status/indication are discussed in Article 6 and **Parts III-V**, respectively.

It is envisaged that persons involved in the manufacture and distribution of traditional medicinal products will be required to hold a valid Manufacturer's and/or Wholesaler's Licence issued by the Irish Competent Authority or the Competent Authority of another EU Member State in accordance with existing legislation in this area – see **Part VII**.

In accordance with the proposed Directive on Traditional Herbal Medicinal Products[10] a 'corresponding medicinal product' as referred to in Article 5.3 (vi) above is characterised by

- same active ingredients, irrespective of excipients used;
- same or similar intended purpose;
- equivalent strength;
- same or similar route of administration

as the medicinal product applied for.

The requirements for the 'expert', in accordance with Article 5.3 (x) above, will be as per Council Directive 75/318/EEC[31] and the proposed Directive on Traditional Herbal Medicinal Products[10]. As such the expert should be a 'suitably qualified and experienced person' and a curriculum vitae, which details such qualifications, and experience should be included in the product registration application. Where the expert is an employee of the company this should be declared. The choice of expert is **at the discretion of the applicant.**

The expert report will be adapted to comply with the International Conference on Harmonisation [ICH] Note for Guidance M4E - Common Technical Document[32] [CTD] once an accepted format for herbal/traditional medicinal products has been agreed. It is suggested that a simplified version of the proposed table of contents for the CTD be required for expert reports accompanying applications under these regulations:

1. Introduction and Background
2. Overview of Traditional Status and Indication Data
3. Overview of Safety
4. Conclusions as to Benefits and Risks
5. References

The ICH is an international co-operation agreed between Europe, the United States of America and Japan whose aim is to harmonise the requirements for the regulation of medicines between the territories. While this group has not looked specifically at traditional medicinal products up to now, we would support such a common regulatory structure for traditional medicinal products.

The requirements for 2. and 3. of the expert report are detailed in **Parts IV-V** of these regulations.

Article 6 Summary of Product Characteristics

The Summary of Product Characteristics [SPC] which must accompany each product registration application should include the following particulars:

(i) the name of the product,

(ii) qualitative and quantitative particulars of all constituents of the product,

(iii) pharmaceutical form,

(iv) clinical particulars:

- traditional use indications,
- posology and method of administration for adults and, where necessary, for children,
- contra-indications,
- special warnings and precautions for use,
- interaction with other medicaments and other forms of interaction,
- use during pregnancy and lactation,
- effects on ability to drive and to use machines,
- undesirable effects [frequency and seriousness],
- overdose [symptoms, emergency procedures, antidotes],

(v) pharmaceutical particulars:

- list of excipients,
- incompatibilities [major],

- shelf-life, when necessary after reconstitution of the product or when the container is opened for the first time,
- special precautions for storage,
- nature and contents of container,
- instructions for use, handling and disposal,

(vi) product registration number,

(vii) name and address of product registration holder and, where applicable, the manufacturer,

(viii) date of first registration or date of renewal,

(ix) date of last revision of text.

EXPLANATORY NOTE TO ARTICLE 6

Article 6 outlines the details required in the SPC or Summary of Product Characteristics. As traditional medicinal products registered in accordance to these regulations are medicinal products but in recognition of the fact that the requirements for such products may be different to conventional medicines, the proposed SPC is adapted from that outlined in the EU SPC Guideline[15] and in the Medicinal products (Licensing and Sale) Regulations, 1998[13].

The SPC forms an important part of the product registration and should in the first instance be prepared by the applicant. Following review of the proposed SPC as part of the product registration assessment, the regulatory authority may require changes to or further justification for certain aspects of the document. At the time of registration, the final agreed SPC is a legally binding contract between the product registration holder and the Competent Authority. This then forms the basis for information in the Patient Information Leaflet [PIL] and information circulated by whatever means to either practitioner groups or the general public.

Where any of the data are not available, the deviation from the above SPC template should be justified by the applicant.

3.5 Part III Quality Assessment

A quality dossier in accordance with Part II of the Rules Governing Medicinal Products in the European Union – Vol. 2B 'Notice to Applicants, Medicinal Products for Human Use, Presentation and Content of the Dossier[33]' is required for all product applications under these regulations [as detailed in Article 7].

EXPLANATORY NOTE

Part III provides that each product registration application submitted under these regulations includes a comprehensive quality dossier. In the interest of consumer safety, it is imperative that traditional medicinal products sold or supplied following registration by the Competent Authority are of the appropriate quality. It is therefore imperative that each product registration application submitted under these regulations includes a quality report. In this way the consumer is assured that the product he/she buys contains what it claims to contain, in the amount it claims to contain and therefore can be expected to act as it is reported to act in accordance with the associated traditional use.

Article 7 Requirements of the Quality Dossier

1. For traditional herbal medicinal products the CPMP/CVMP 'Note for Guidance on Quality of Herbal Medicinal Products[9]' will apply. This should be read in conjunction with Annex 7 to the Good Manufacturing Practices Guideline 'Good Manufacturing Practices – Medicinal products for human and veterinary use' from Vol. 4, Rules Governing Medicinal Products in the European Union[34]; GMP recommendations should be observed in full.

   In addition, the CPMP/CVMP 'Note for Guidance on Specifications: Test Procedures and Acceptance Criteria for Herbal Drugs, Herbal Drug Preparations and Herbal Medicinal Products[35]' will apply.

2. For traditional non-herbal medicinal products, analogous requirements to ensure the quality of such products will be drawn up in due course. In the interim, GMP recommendations should be observed.

EXPLANATORY NOTE TO ARTICLE 7

In relation to Article 7.1 it should be noted that many of the reported adverse reactions relating to herbal medicinal products are due to misidentification/adulteration of the herbal substance. The guidance documents on quality and testing cited were developed by the Herbal Medicinal Products Working Party [HMPWP] of the European Medicines Evaluation Agency [EMEA], a committee of acknowledged experts in the area. On 1st July 2001, these guidelines were adopted by the EMEA Committee on Proprietary Medicinal Products [CPMP] and the Committee on Veterinary Medicinal Products [CVMP].

It is acknowledged that similar guidelines need to be developed for non-herbal substances/products.

3.6 Part IV Safety Assessment

The safety of a medicinal product subject to registration under these regulations will be determined by reference to all available data, both favourable and unfavourable, presented as outlined below.

EXPLANATORY NOTE

In order to effectively assess the safety of a medicinal product it is necessary to review all available data. The purpose of such an assessment is to determine whether the product in question is safe for use by the consumer under the normal conditions of use. It is acknowledged that additional data may emerge following issuance of a product registration. Under such circumstances, product registrations may be subject to review. Where such data highlight a potential risk to public safety, the Competent Authority reserves the right to suspend or revoke a product registration or to initiate a product recall.

Article 8 Evaluation of Safety

1. In the absence of clinical or toxicological data, the safety of a product may be determined primarily by reference to bibliographic data.

2. Such bibliographic data should include any available post-marketing surveillance data and periodic safety update reports [PSURs] collated as part of a formal pharmacovigilance system. Such systems will be mandatory for all product registration holders once these regulations are in place [see Article 22].

3. Bibliographic data should be justified, validated and prioritised by the applicant's chosen expert.

EXPLANATORY NOTE TO ARTICLE 8

Article 8 provides that any person seeking to register a product under these regulations must provide evidence that the product is safe for the consumer and does not, in any way, pose a risk to public health.

Acceptable bibliographic sources of such information include but are not restricted to:

- WHO Monographs,
- ESCOP Monographs,
- Published articles from reputable scientific journals,
- Reviews by recognised medicinal product regulatory agencies,
- Relevant reference texts.

Post-marketing surveillance data and PSURs must, where available, be presented as part of the safety assessment. Intrinsic to the registration scheme will be a requirement that the product registration holder establishes a formal system through which the safety of registered products can be monitored and reported to the regulatory authority.

The IMB will extend its existing pharmacovigilance system to accommodate traditional medicinal products registered under these regulations – see Article 22.

3.7 Part V Assessment of Traditional Status and Claim

Persons seeking to register a product under these regulations will provide evidence that the product has a traditional status as per Article 4. In addition the applicant will be required to provide bibliographic evidence in support of the proposed traditional use claim.

EXPLANATORY NOTE

Part V of these regulations provides that in order to register a product under these regulations the applicant must provide evidence that the product, or a corresponding product [see Article 5], meets the requirements for proof of tradition as laid down in Article 4.1.

In addition, the applicant must show that the traditional use indication can be substantiated and is therefore truthful. In this way the consumer can be assured that the product will, in accordance with the tradition of practice, be effective for the indication claimed.

Article 9 Evaluation of Traditional Use

The applicant must provide evidence that the product in question or a corresponding product [see Article 5] is a 'traditional' medicinal product as defined in Article 2.1 as follows:

1. Bibliographic data shall provide evidence that the product has been in continuous medicinal use in the Community for a period of 30 years preceding the date of application, or

2. Bibliographic data shall provide evidence that the product has been in continuous medicinal use in another specified territory or partly in such a territory and partly in an EU Member State for 30 years preceding the date of application and 15 years in an EU Member State, and

3. The application should be accompanied by an expert evaluation of the reference(s) provided.

EXPLANATORY NOTE TO ARTICLE 9

In accordance with Article 9.1 bibliographic evidence of 'traditional use' is defined as one or more documented references, which could include but is not limited to:

- Published articles from conventional or traditional medical journals,
- Pharmacopoeial monographs dating from 30 years ago or more,
- Advertisements in recognised journals, newspapers or magazines,
- Wholesaler/manufacturer catalogues.

In all cases a copy of the cited reference(s) should be included with the application. A specific list of acceptable references will be compiled by the Competent Authority as part of a guideline to these regulations.

In addition to the above, the application should be accompanied by a critical evaluation and validation of the chosen reference(s) carried out by the applicants chosen expert. It is acknowledged that a degree of flexibility with regard to the requirement for more than one reference should exist particularly where the evidence presented is compelling. In such cases, the expert report will be critical.

Article 10 Evaluation of the Traditional Indication Claim

The traditional indication claim for a product is chosen by the applicant. Such a claim should be supported by bibliographic evidence as defined below. Medicinal products registered under these regulations shall be available for sale in pharmacies only or will be available for general sale.

1. Evidence in support of a traditional indication claim shall be:

   (i) Three references from conventional or traditional medical literature, and

   (ii) EU recognised pharmacopoeial monographs, where applicable, or

   (iii) Other monographs recognised by the Competent Authority.

2. An expert report providing a critical evaluation of all data provided.

EXPLANATORY NOTE TO ARTICLE 10

The route of sale of a medicinal product registered under these regulations will be determined on a case-by-case basis at the time of assessment of the product registration application and will be determined based on the safety of the individual product concerned.

In the interest of consumer protection, Article 10 provides that the traditional indication claim as proposed by the applicant can be supported by reference to bibliographic evidence and can therefore be shown to be both accurate and truthful.

As part of a guideline to these regulations a list of acceptable references will be compiled by the Competent Authority. Any such list will not be restrictive and once a reference is justified, this will be considered by the Competent Authority and the proposed Sub-Committee on Traditional Medicinal Products [see Article 15] for inclusion on such a list.

Sources of EU recognised monographs include but are not restricted to:

- European Pharmacopoeia,
- Other EU National Pharmacopoeias,
- British Herbal Pharmacopoeia,
- United States Pharmacopoeia and National Formulary,
- Martindale: the Extra Pharmacopoeia,
- EU National Pharmaceutical Codices,
- Japanese Pharmacopoeia,
- Pharmacopoeia of the People's Republic of China.

Additional recognised monographs include but are not restricted to:

- ESCOP Monographs,
- WHO Monographs,
- German Commission E Monographs,
- Other EU herbal Monographs [cf. Article 8 of the proposed Directive on Traditional Herbal Medicinal Products[10]].

The expert evidence shall consist of a critical evaluation of the traditional use data for the product and of investigations carried out on animals or humans, where available, and shall bring out all data relevant for evaluation. It shall be worded so as to enable the reader to obtain a good understanding of the basis for the traditional use claim as well as the advantages and disadvantages of the product.

3.8 Part VI Final Provisions

Article 11 Refusal of Product Registration

The registration of a product under these regulations can be refused if, for example:

1. The product does not meet the requirements of these regulations,
2. The qualitative and/or quantitative composition is not as declared,
3. The proposed therapeutic indication does not comply with the requirements of these regulations and/or specifies a condition or disease as outlined in the Medical Preparations (Advertising) Regulations 1993[7], as amended,
4. The product could be harmful under normal conditions of use,
5. Information on traditional use is insufficient, especially if pharmacological effects or efficacy are not plausible on the basis of long-term use and experience,
6. The product would be classed as a medicinal product subject to medical prescription as per Medicinal Products (Prescription and Control of Supply) Regulations, 1996[14], as amended,
7. The product is other than an oral, external or inhalation preparation,
8. The pharmaceutical quality is not satisfactorily demonstrated.

EXPLANATORY NOTE TO ARTICLE 11

The provisions of Article 11 are in line with Council Directive 65/65/EEC[8] and the proposed Directive on Traditional Herbal Medicinal Products[10]. It should be pointed out that it is not possible to define exact criteria for refusal of a registration application. The above provide examples of certain instances when such a measure may be necessary. This list should not be considered restrictive.

The standard operating procedure [SOP] for refusal of authorisations as amended [see **Appendix 11**] shall apply to medicinal products registered under these regulations.

Article 12 Suspension/Revocation of Product Registration

A product registration issued under these regulations may be suspended or revoked if, for example:

1. The product registration holder fails to comply with any conditions of the registration,

2. New safety data highlight a potential threat to public health.

EXPLANATORY NOTE TO ARTICLE 12

In order to safeguard public health, Article 12 provides that the Competent Authority has the authority to suspend or revoke a product registration. Suspensions and revocations of product authorisations for conventional medicines are currently dealt with on a case-by-case basis. Similarly, suspensions and revocations of traditional medicinal product registrations will be dealt with as the situations arise.

It is acknowledged that it is not possible to detail every reason that a registration may be suspended or revoked, except to state that such a provision will only be implemented where necessary.

It is the intention to develop Standard Operating Procedures [SOPs] for suspending/revoking product authorisations/registrations, similar to that for rejections. Such SOPs will cover both conventional medicines licensed under Council Directive 65/65/EEC[8] and traditional medicinal products registered under these regulations.

Article 13 Appeals Procedure

The applicant will be provided with an opportunity to appeal any decision taken by the Competent Authority to refuse, suspend or cancel a product registration.

EXPLANATORY NOTE TO ARTICLE 13

In line with the current practice for conventional medicines for appealing the decisions of the IMB, each appeal under the proposed interim national licensing scheme for traditional medicinal products will be dealt with on a case-by-case basis.

It is the intention to develop a Standard Operating Procedure [SOP] for appeals of product authorisation/registration rejections, suspensions and/or revocations, in line with the provisions of Article 12 of Council Directive 65/65/EEC[8] and the proposed Directive on Traditional Herbal Medicinal Products[10]. Any such SOP will cover traditional medicinal products registered under these regulations.

Article 14 Traditional Medicinal Products Unit

A unit dedicated to the evaluation of applications for product registration under these regulations shall be set up within the Competent Authority. This unit will be adequately resourced and staffed so that it has pharmaceutical, medical and herbal assessors.

EXPLANATORY NOTE TO ARTICLE 14

The *ad hoc* SCHMP is of the opinion that the IMB in its capacity as the Competent Authority responsible for the licensing of manufacture, preparation, importation, distribution and sale of medicinal products in Ireland[1], is the most appropriate regulatory body to assume responsibility for the registration of traditional medicinal products and the associated requirements of such a registration as proposed in these regulations. The creation of a separate regulatory authority, which has been proposed and considered, would, in the opinion of the SCHMP, pose additional organisational difficulties and therefore significant associated costs.

In order to take on the responsibility for these regulations, it will be necessary to fully resource a unit within the IMB committed to implementing these regulations and ensuring that traditional medicinal products available on the Irish market are registered and fully compliant with any such registration. In addition it will be necessary to supplement the resources of other IMB Departments to cover the associated increase in their workload i.e. Medical including Pharmacovigilance, Pharmacy, Inspectorate, Enforcement and Administration.

Article 15 Sub-Committee on Traditional Medicinal Products

A Sub-Committee of the IMB Advisory Committee on Human Medicines [ACHM] shall be established. The chairperson shall be appointed to the ACHM. The membership of this new committee should closely reflect the membership of the *ad hoc* SCHMP and should include individuals with *inter alia* expertise in:

- Medical Herbalism
- Medicine
- Pharmacy
- Pharmacognosy
- Toxicology
- Aromatherapy
- Traditional Chinese Medicine
- Complementary Medicine in General

The Terms of Reference should include the provision of advice on the implementation of these regulations; monitoring the implementation of these regulations; establishment of national lists of approved indication claims and approved bibliographic sources which could be used to support the claims; approval of any positive or negative lists which might be prepared and the general provision of advice and technical back up to the staff of the Traditional Medicines Unit.

EXPLANATORY NOTE TO ARTICLE 15

It is the opinion of the SCHMP that a Sub-Committee on Traditional Medicinal Products should be established within the current IMB structure and in accordance with the Irish Medicines Board Act 1995[2]. This sub-committee will deal exclusively with issues relating to traditional and, where applicable, herbal medicinal products. It will be established as a Sub-Committee to the IMB Advisory Committee on Human Medicines [ACHM], and its chairperson will sit on that Committee.

It should be noted that the IMB/SCHMP considered the possibility of recommending that an Advisory Committee on Traditional Medicine be established. However, as this would involve a change in primary legislation, it was not considered to be a practical option. In addition the IMB/SCHMP considered that the establishment of a Sub-Committee acknowledged the increased consumer use of these products but also correctly reflected their status as human medicines, on a par with all other human medicines currently evaluated by the IMB.

Article 16 Implementation

1. The Competent Authority shall comply with these regulations at such a time as the Department of Health and Children directs it to do so.

2. Persons responsible for putting traditional medicinal products [as defined in Article 2] on the market in Ireland at the time of entry into force of these regulations shall inform the Competent Authority of the details of such products within three months. Such persons will be required to submit an application for registration of such products to the Competent Authority within six months of entry into force of these regulations. Products not so notified shall be removed from the market.

3. The Competent Authority will apply the provisions of these regulations within three years after their entry into force.

4. Persons responsible for the marketing of traditional medicinal products shall, within three years after entry into force of these regulations, comply fully with the requirements of **Part VII** of these regulations.

EXPLANATORY NOTE TO ARTICLE 16

Article 16 details the proposed timelines for implementation of and compliance with these regulations for both the Competent Authority and product registration holders. Such provisions will ensure that traditional medicinal products available on the Irish market will be evaluated and registered by the Competent Authority in as short a period as possible. This will ensure that those products available for sale to the consumer are of appropriate quality, safe and have a proven tradition of use for the indication claimed.

It is acknowledged that the evaluation of a large number of product registration applications will take a considerable amount of time. It is therefore envisaged that once an application has been submitted to the Competent Authority within the above timeline, such products will be allowed to remain on the market during the evaluation period providing, in the view of the Competent Authority, there is no associated risk to public health.

3.9 Part VII Additional Provisions

The following provisions relate to traditional medicinal products registered under these regulations and the product registration holders. The provisions as outlined in Articles 17-22 are adapted from existing legislation for conventional medicines in the relevant areas and, where appropriate, the proposed Directive on Traditional Herbal Medicinal Products[10].

Article 17 Labelling

1. The following should appear on the outer packaging:

   a.) the product is a traditional use medicinal product for use in a specified indication and that the efficacy of the product has not been clinically proven but relies exclusively on long-term use and experience,

   b.) the user should consult a doctor or a qualified practitioner if symptoms persist during the use of the medicinal product,

   c.) the name of the product followed by the Latin or other accepted scientific name where the product contains a single active substance; where a product is available in a number of strengths or forms this information should also be included,

   d.) a statement of the active ingredients [i.e. herbal substance – including the Latin names and plant part, where appropriate] expressed, where possible, qualitatively and quantitatively,

   e.) the pharmaceutical form and, where possible, the contents by weight, volume or number of doses,

   f.) the method and route of administration,

   g.) a warning to 'store out of reach of children',

   h.) other specific warnings for the product concerned,

   i.) the expiry date,

   j.) special storage conditions if required,

   k.) the name and address of product registration holder,

   l.) the registration number,

   m.) the batch number,

   n.) instructions for use of the product,

o.) the statement 'Do not exceed the stated dose'.

2. The above information shall appear on the immediate packaging except in the following cases:

2.1 Blister packs:

a.) the name of the product followed by the Latin or other accepted scientific name where the product contains a single active substance; where a product is available in a number of strengths and forms this should also be included,

b.) the name of the registration holder,

c.) the expiry date,

d.) the batch number.

2.2 Where immediate packaging is too small:

a.) the name of the product and where necessary, the strength and route of administration,

b.) the method of administration,

c.) the expiry date,

d.) the batch number,

e.) where possible, the contents by weight, volume or unit dose.

3. Information shall be clearly legible and shall appear in English. The particulars may, in addition, indicate the specific tradition from which the product originates and appear in the language of that tradition.

4. The above requirements will be mandatory from the date of entry into force of these regulations; all registration holders will be required to comply with these requirements within three years.

5. The above requirements shall not apply to a traditional medicinal product that is:

a.) sold or supplied by a registered practitioner for or to a patient under their care.

b.) sold or supplied by a person lawfully keeping open shop for the dispensing or compounding of medical prescriptions or for the sale of poisons under the

Pharmacy Acts, 1875-1977[36] where such a sale is carried out and the product is extemporaneously compounded by or under the supervision of a pharmacist for such particular sale.

6. Traditional medicinal products sold or supplied in accordance with Article 17.5 of these regulations should be labelled in accordance with the requirements for a 'dispensed medicinal product' as per the Medicinal Products (Prescription and Control of Supply) Regulations, 1996[14], as amended.

EXPLANATORY NOTE TO ARTICLE 17

This Article is designed to look at the labelling requirements for traditional medicinal products registered under these regulations. The requirements are in line with those for other medicinal products as per the Medical Preparations (Labelling and Package Leaflet) Regulations, 1993[12], as amended and the draft Directive on Traditional Herbal Medicinal Products[10].

It is in the interest of public safety that products registered under these regulations, and provided to the consumer for self-medication, are adequately labelled with all the information required by the patient to use the product safely. Attention is also drawn to the Readability Guideline[37] which is designed to ensure that the label is accessible to all those with a reading age of 11 years and above.

Article 18 Patient Information Leaflets

1. The following should appear in the Patient Information Leaflet [PIL]:

a.) the product is a traditional use medicinal product for use in a specified indication and that the efficacy of the product has not been clinically proven but relies exclusively on long-term use and experience

b.) the user should consult a doctor or a qualified practitioner if symptoms persist during the use of the medicinal product

c.) the name of product followed by the Latin or other accepted scientific name where the product contains a single active substance; where a product is available in a number of strengths or forms this information should also be included,

d.) a full statement of active substances [i.e. herbal substance - including Latin names and plant part, where appropriate], and excipients expressed qualitatively and quantitatively,

e.) the form and contents of the product by weight, volume or number of doses,

f.) the name and address of the product registration holder and the product manufacturer, where these differ,

g.) traditional use claims - to appear in English and if required, the language of the specific tradition,

h.) contra-indications,

i.) interactions, where known,

j.) special warnings,

k.) the dosage,

l.) the method and route of administration,

m.) the duration of treatment,

n.) the action to be taken in the event of overdose, where appropriate/known,

o.) a description of undesirable effects which can occur under normal conditions of use; the user should be specifically invited to report any undesirable effects to his/her registered practitioner, pharmacist or the registration holder,

p.) the expiry date,

q.) any special storage conditions,

r.) date of last revision of the package leaflet,

s.) the statement 'Do not exceed the stated dose'.

2. Information shall be clearly legible and shall appear in English. The particulars may, in addition, indicate the specific tradition from which the product originates and appear in the language of that tradition.

3. The inclusion of a patient information leaflet shall be obligatory unless the required information appears on the outer packaging of the product.

4. The above requirements will be mandatory from the date of entry into force of these regulations; all registration holders will be required to comply with these requirements within three years.

5. The above requirements shall not apply to a traditional medicinal product that is:

   a.) sold or supplied by a registered practitioner for or to a patient under their care.
   b.) sold or supplied by a person lawfully keeping open shop for the dispensing or compounding of medical prescriptions or for the sale of poisons under the Pharmacy Acts, 1875-1977[36] where such a sale is carried out and the product is extemporaneously compounded by or under the supervision of a pharmacist for such particular sale.

6. Traditional medicinal products sold or supplied in accordance with Article 17.5 of these regulations should be labelled in accordance with the requirements for a 'dispensed medicinal product' as per the Medicinal Products (Prescription and Control of Supply) Regulations, 1996[14], as amended.

EXPLANATORY NOTE TO ARTICLE 18

This Article outlines the details that should appear on the patient information leaflet [PIL] accompanying the product. The PIL shall be drawn up in accordance with the SPC [see Article 6] as agreed between the registration holder and the Competent Authority.

The above requirements are in line with the Medical Preparations (Labelling and Package Leaflets) Regulations, 1993[12], as amended and the draft Directive on Traditional Herbal Medicinal Products[10] and are designed to ensure that the patient is accurately and fully informed about the product they are taking.

Attention is also drawn to the Readability Guideline[37] which is designed to ensure that the patient information leaflet is accessible to all those with a reading age of 11 years and above.

Article 19 Advertising

1. The provisions of the Medical Preparations (Advertising) Regulations, 1993[7] as amended shall likewise apply to traditional medicinal products registered in accordance with these regulations.

2. In accordance with the draft Directive on Traditional Herbal Medicinal Products[10] the following shall also appear in any advertising for a traditional medicinal product registered in accordance with these regulations:

   a.) the product is a traditional use medicinal product for use in a specified indication and that the efficacy of the product has not been clinically proven but relies exclusively on long-term use and experience,

   b.) the user should consult a doctor or a qualified practitioner if symptoms persist during the use of the medicinal product.

EXPLANATORY NOTE TO ARTICLE 19

The provisions of Article 19.1 would prohibit the advertising of a traditional medicinal product in respect of which a product registration has not been granted. Advertising shall comply with the SPC [see Article 6] and shall therefore be product specific. Any advertisement for a traditional medicinal product shall conform to that outlined in Schedule 2 of the Medical Preparation (Advertising) Regulations, 1993[7] reproduced verbatim below:

Format of the advertisement:
The advertisement must be set out in such a way that it is clear that the message conveyed is an advertisement.

The advertisement shall contain:

a.) A clear indication by name that the product being advertised is a herbal/traditional medicinal product.

b.) The information necessary for the correct use of the herbal/traditional medicinal product.

c.) A warning to read carefully the instructions on the package leaflet or on the outer packaging as the case may be.

The advertisement shall not contain any material which:

b.) gives the impression that a medical consultation or surgical operation is not necessary, in particular offering a diagnosis or by suggesting treatment by mail,

c.) suggests that the effects of taking the medicine are guaranteed, are unaccompanied by side effects or are better than, or equivalent to, those of another treatment or medicinal product,

d.) suggests that the health of the subject can be enhanced by taking the medicine*,

e.) suggests that the health of the subject could be affected by not taking the medicine,

f.) is directed exclusively or principally at children,

f.) refers to a recommendation by scientists, health professionals or persons who are neither of the forgoing but who, because of their celebrity, could encourage the consumption of medicinal products,

g.) suggests that the medicinal product is a foodstuff, cosmetic or other consumer product,

h.) suggests that the safety and efficacy of the medicinal product is due to the fact that it is natural,

i.) could, by description or detailed representation of a case history, lead to an erroneous diagnosis,

j.) refers, in improper, alarming or misleading terms, to claims of recovery,

k.) uses, in improper, alarming or misleading terms, pictorial representations of changes in the human body caused by disease or injury, or of the action of a medicinal product on the human body or parts thereof,

l.) mentions that the medicinal product has been granted a marketing authorisation.

*** NOTE: The IMB and its *ad hoc* SCHMP note that the provisions of c.) above may place an unnecessary restriction on claims that can otherwise be justified for traditional medicinal products and recommend that this be reviewed further by the Department of Health and Children.**

Article 20 Manufacturer's Licences and Compliance with GMP

1. Any person involved in the manufacture of a traditional medicinal product registered in accordance with these regulations is required to hold a Manufacturer's Licence issued by the Competent Authority in accordance with Council Directives 75/319/EEC[38] and 91/356/EEC[39] and associated Irish legislation [Medical Preparations (Licensing of Manufacture) Regulations, 1993[40] as amended] or by the Competent Authority of another EU Member State in accordance with the national legislation of the Member State concerned.

2. Any person involved in the importation from a country outside the European Economic Area [EEA] of a traditional medicinal product is required to hold a Manufacturer's Licence issued by the Competent Authority in accordance with Council Directives 75/319/EEC[38] and 91/356/EEC[39] and associated Irish legislation [Medical Preparations (Licensing of Manufacture) Regulations, 1993[40]

as amended] or by the Competent Authority of another EU Member State in accordance with the national legislation of the Member State concerned.

EXPLANATORY NOTE TO ARTICLE 20

A Manufacturer's Licence is required for each location where a traditional medicinal product is manufactured or packaged. This licence will detail the activities permitted at the site for which it is issued. It is the recommended that the IMB or the Competent Authority of another EU Member State should be responsible for issuing such a Manufacturer's Licence.

The provisions of Article 20.1 are designed to ensure that any person seeking to register a product under these regulations is carrying out the manufacture of such a product in accordance with standards of Good Manufacturing Practice [GMP] as per Rules Governing Medicinal Products in the European Union Vol. 4 'Good Manufacturing Practices – medicinal products for human and veterinary use'[34] with additional reference to Annex 7. GMP requirements cover standards of quality management, personnel, premises and equipment, documentation and record keeping, production, quality control, contract manufacture as well as complaints, product recall and self-inspection.

The provisions of Article 20.2 are designed to ensure that any traditional medicinal product imported from outside the EEA is retested in Ireland or another Member State prior to being placed on the market. Such sites would also be required to adhere to the GMP Guidelines[34] cited above.

As part of the evaluation of a licence application, a site inspection carried out by the Inspectorate Department of the IMB, will be required to ensure compliance with GMP standards. Samples of any material used in the manufacture process should be provided for examination or analysis on request. In addition, the Inspectorate Department of the IMB may require to inspect any non-EEA based manufacturing site.

The IMB/SCHMP recommend that registered medical practitioners, registered dentists, registered pharmaceutical chemists or qualified practitioners [cf. proposed Directive on Traditional Herbal Medicinal Products[10]] would not be required to hold a Manufacturer's Licence for the preparation or supply of medicinal products registered under these regulations to patients under their care.

In the interest of public safety, the Competent Authority will have the authority to suspend or revoke a Manufacturer's Licence. This provision may be used where a licence holder contravenes the conditions of the licence or where issues of safety arise.

Article 21 Wholesaler's Licence and Compliance with GDP

Any person involved in the wholesale and distribution of a traditional medicinal product registered in accordance with these regulations is required to hold a Wholesaler's Licence issued by the Competent Authority in accordance with Council Directives 75/319/EEC[38] and 92/25/EEC[41] and associated Irish legislation [Medical Preparations (Wholesale Licences) Regulations, 1993[16] as amended].

EXPLANATORY NOTE TO ARTICLE 21

A Wholesaler's Licence is required for any locations from where a traditional medicinal product is distributed. This licence will detail the activities permitted at the site for which it is issued. It is the recommended that the IMB should be responsible for issuing such a Wholesaler's Licence.

The provisions of Article 21 are designed to ensure that any person responsible for the wholesale and distribution of a traditional medicinal product carries out this activity in accordance with standards of Good Distribution Practice [GDP] as per the EU Guidelines on Good Distribution Practice of Medicinal Products for Human Use[42]. GDP requirements cover standards of personnel, documentation, premises and equipment, deliveries, returns and self-inspection.

As part of the evaluation of a product application, a site inspection carried out by the Inspectorate Department of the IMB will be required in order to ensure compliance with GDP standards[42]. Samples of any materials stored or distributed on the site should be provided for examination or analysis on request.

In the interest of public safety, the Competent Authority will have the authority to suspend or revoke a Wholesaler's Licence. This provision may be used where a licence holder contravenes the conditions of the licence or where issues of safety arise.

Article 22 Pharmacovigilance

1. The established conventional system of pharmacovigilance as per Council Directive 75/319/EEC[38] and Council Regulation 2309/93[43] will likewise apply to traditional medicinal products registered in accordance with these regulations,

unless specific herbal legislation is defined which addresses pharmacovigilance of herbal medicinal products.

2. Each product registration holder will be required to establish a formal pharmacovigilance system in accordance with the above legislation.

3. A formal reporting system for registered practitioners, including herbal practitioners will be established.

EXPLANATORY NOTE TO ARTICLE 22

Article 22 is designed to ensure that the safety of all products registered under these regulations is monitored on an ongoing basis. To this end each product registration holders will be required to have a system for monitoring adverse events that occur through the use of the product and/or interactions with other conventional and/or traditional medicinal products and to report any such events to the IMB. Intrinsic to such a system is the provision that the registration holder provides the IMB with Periodic Safety Update Reports [PSURs] on each product registered. In addition, a reporting mechanism for all registered practitioners, modelled on that in existence for conventional medicines, will be established.

It is recommended that the IMB Pharmacovigilance Unit will be responsible for monitoring and processing all reports received by the IMB and action will be taken on the basis of evaluation of such reports by that Unit, in consultation with the Traditional Medicines Unit as proposed in Article 14.

Given the need to implement the requirements of these regulations and to establish reporting systems and procedures with companies, healthcare professionals and herbal practitioners, additional resources will be necessary in order to incorporate traditional medicinal products into the current system.

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APPENDICES

Appendix 1 Letter from the Minister for Health and Children to initiate a Herbal Medicines Project

23 June, 2000

DEPARTMENT OF HEALTH AND CHILDREN
AN ROINN SLAINTE AGUS LEANAI

Shaping a Healthier Future

Dr. Frank Hallinan,

Chief Executive,
Irish Medicines Board,
Earlsfort Centre,
Earlsfort Terrace,
Dublin 2.

Dear Dr. Hallinan,

In accordance with paragraphs (j) and (n) of Section 4(1) of the Irish Medicines Board Act, 1995 (No 29 of 1995), I am directed by the Minister to request that your Board advise the Minister in relation to the nature of a scheme that might be introduced in this country in respect of the licensing of "traditional and alternative" medicinal products, including herbal medicinal products.

I am to point out that under current EU legislation relating to the authorisation of medicinal products, the full requirements of quality, safety and efficacy must be complied with before an authorisation may be granted. I am therefore to state that the Minister is prepared to consider the introduction of an appropriate national scheme for the authorisation of ''traditional" or "alternative" medicinal products, including herbal medicinal products, on the basis of a standard other than that which currently applies to medicinal products generally. Obviously, any such scheme would have to be provided for by means of Regulations.

I am to point out that any national scheme of this nature for the authorisation of medicinal products must-

(a) adequately define the medicinal products to which it relates;
(b) adequately address the standards of quality and safety, and
(c) where the standard proof of efficacy has not been met, the products concerned should-

    (i) be appropriately identifiable,
    (ii) where medicinal claims-are made, be such that any such claims in respect of the use of such product are appropriate having

regard to the fact that the standard proof of efficacy has not been met; and

(iii) be otherwise such that the interests of public health are adequately protected.

I am also to state that any scheme of this nature must of necessity have to be on an interim basis pending the introduction of appropriate EU measures when full authorisation of such products will be required on the basis of whatever requirements are to be eventually agreed.

I am to request that your Board report back to this Department in this matter as early as possible. If it is not possible to submit its final report within a period of three months of the date of this letter, I am to request that an interim report in the matter be provided not later than the end of that period.

Yours sincerely,

Noel P Usher
Principal

Hawkins House Dublin 2
Teach Haicin Bade Atha Cliath 2
Telephone (0 I) 635 4000 VPN 112
Telex 3345 I Fax (01) 635 4001

Appendix 2 National Press Advertisement

Regulation of 'traditional and alternative' medicinal products including herbal medicinal products in Ireland

The Irish Medicines Board has been charged with the responsibility of developing a proposal for a national licensing scheme for 'traditional and alternative' medicinal products, including herbal medicinal products on behalf of the Department of Health and Children. It is proposed that as part of the process, a scientific committee be established whose members will be experts in this area.

In addition to this and in line with the policy of the Irish Medicines Board, we would like to consult with all interested parties, including members of the public. Submissions on this issue should preferably address the following topics : -

- The Scope of a National Licensing Scheme

  The kinds of products which should be regulated under such a scheme i.e. definition and/or categorisation of traditional, alternative and herbal medicinal products.

- The Development Process

  The mechanisms by which such a licensing system could be established bearing in mind the role of the Irish Medicines Board and the current national and European legislation. The role of a scientific panel of experts and suggestions for possible members of such a panel should also be addressed.

- The New System

  The specific issues that should be considered in a framework document should include at least the following : -

  quality,

  safety,

efficacy,
adverse event reporting,
quality defect reporting
packaging & labelling,
advertising,
product licensing.

- Any other relevant information or proposals which the correspondent deems appropriate.

Submissions should be sent by e-mail to *imb@imb.ie* or by post to Herbal Medicines Project Manager, Irish Medicines Board, Earlsfort Centre, Earlsfort Terrace, Dublin 2.

The closing date for receipt of submissions is **Tuesday 31st October 2000**. For further information contact the Herbal Medicines Project Manager at (01) 6764971.

Appendix 3 Advertisement Responses

1. Mr. D. McDonnell, Individual member of the public,
2. Mr. Luke Bracken, Individual member of the public,
3. Mr. Bob Conway, Individual member of the public,
4. Mr. Jonathan Griffith, Natural Medicine Company,
5. Mr. Rory O'Riordan, Clonmel Healthcare/A Stada Group Company,
6. Mr. R. Dalton, Individual member of the public,
7. Ms. Judith Hoad, Individual member of the public/member of the Irish Association of Medical Herbalists,
8. Mr. Matt Ronan, Individual member of the public/Health food store owner,
9. Mr. J. Denzinger, Individual member of the public/Health food store owner,
10. Ms. Geraldine Lavelle, The International Society of Profesional Aromatherapists - Irish Branch,
11. Mr. Martin Murray, Irish Health Trade Association,
12. Ms. Monica Mackin, Tara School of Integrative Therapies,
13. Ms. Claudine Hughes, National Medicines Information Centre,
14. Mr. A. Cavanagh, Individual member of the public,
15. Ms. Breda Dooley, Consumers for Health Choice Ireland,
16. Dr. Rosemary Barry/Dr. Maurice Colins, PAC Laboratories,
17. Ms. J. Parfrey, North West Women's Network and South Sligo Women's Group
18. Ms. D. Kennan, Irish Association of Medical Herbalists,
19. Mr. P. Geoghgan, Individual member of the public,
20. Ms. J. Lahiff, Individual member of the public,
21. Prof. Brendan O'Mahony, Individual member of the public/Academic,
22. Ms. Helen McCormack, Irish Herbal Practitioners' Association [incorporating the Irish Association of Medical Herbalists and the Irish Register of Chinese Herbal Medicine],
23. Ms. Alison Denham, National Institute of Medical Herbalists, UK,
24. Ms. Rosari Kingston, Individual member of the public/Herbalist,

25. Ms. R. Woollen, Peter Black Healthcare Ltd.,

26. Ms. Nicola Darrell, Irish and International Aromatherapy Association's,

27. Mr. Alan Sheehy, Southern Kingdom Herbs Ltd.,

28. Ms. K. McBride/Ms. M. Plunkett, The Professional Register of Chinese Herbal Medicine/The Professional Register of Traditional Chinese Medicine/The Irish College of Traditional Chinese Medicine,

29. Mr. Michael McIntyre, The European Herbal Practitioners Association,

30. Ms. Teresa Graham, Individual member of the public,

31. Mr. Brod Kearon, Irish Association of Health Stores,

32. Mr. J. Roche, Individual member of the public/Academic,

33. Dr. Dilis Clare/Ms. Anna-Maria Keaveney, Individual members of the public/members of the IAMH,

34. Ms. Sally Quinlan, The Irish Society of Homeopaths,

35. Dr. Paul Tomkins, Individual member of the public/Academic,

36. Mr. Brendan Duffy, Irish Organic Herbs,

37. Mr. David Keogh, Individual member of the public/Herbalist,

38. Dr. Maureen Murphy, Individual member of the public,

39. Mr. Ian & Mrs. Lynn Wright, Individual members of the public,

40. Mr. Ger Roberts, Clonmel Healthcare Limited/A Stada Group Company,

41. Mr. Ralph Quinlan Forde, Individual member of the public/Herbalist.

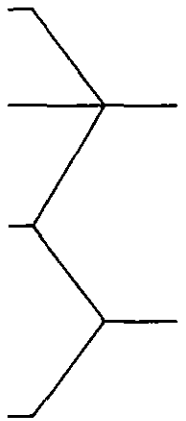
Appendix 4 Interested Organisations

Irish Association of Health Stores [IAHS] - Sally Smith

Irish Health Trade Association [IHTA] - Martin Murray

Irish Association of Medical Herbalists [IAMH] - Helen McCormack *

Irish Register of Chinese Herbal Medicine [IRCHM] - David Foley



Health Product Alliance [HPA] - Jonathan Griffith

Irish Herbal Practitioners Association [IHPA] -Helen McCormack

Professional Register of Traditional Chinese Medicine [PRTCM] - Alan Sheehy/Mary Plunkett

Consumers for Health Choice [CHC] - Breda Dooley

* The IAMH is the only agency with an affiliation to more than one umbrella body

Appendix 5 Terms of Reference of the SCHMP

1.1 Function:

To advise and assist the Board in relation to any matters pertaining to the development of a proposal for the licensing of 'traditional and alternative' medicinal products including herbal medicinal products for human use.
To advise the Board in relation to any proposed legislative framework for such products.

1.2 Membership:

The 9 members are experts in herbal medicine and related areas and are appointed by the Chairperson.

The Chairperson will be Dr. Desmond Corrigan, Director, School of Pharmacy, Trinity College, Dublin 2.

1.3 Frequency of Meetings:

Meetings shall be as deemed necessary by the Chairperson.

1.4 Reporting of Outcomes:

The outcomes are reported in the Scientific Committee on Herbal Medicinal Products minutes.

Appendix 6 Confidentiality & Declaration of Interest of the SCHMP

6.1 Confidentiality Agreement

CONFIDENTIALITY AGREEMENT

In discharging its statutory function the Irish Medicines Board deals with highly confidential matters, including information on patients' reactions to drugs and pharmaceutical company formulations in medicines.

An adviser/expert of the Board, its Committees/Sub-Committees or Working Parties is prohibited from disclosing any confidential information obtained in his/her capacity as an adviser/expert of the Board. In addition, records/documentation must never be left in such a manner that unauthorised persons can obtain access to them.

I, , agree to be bound by this confidentiality agreement.

Signed: _____

Dated: _____

* Includes the manufacture, importation or distribution of herbal, alternative and/or traditional medicinal product

6.2 Public Declaration of Conflicts of Interest

PUBLIC DECLARATION OF INTERESTS OF THE MEMBERS OF COMMITTEES/SUB-COMMITTEES, WORKING PARTIES AND EXPERTS

Name: _____

Qualifications: _____

Professional Address:_____

_____

Please list below all interest in the pharmaceutical* industry if any:

1. Employment in the pharmaceutical industry during the previous 5 years

_____

2. Financial interests in the capital of a pharmaceutical company:

_____

3. Work currently or previously carried out by yourself in return for payment on behalf of the pharmaceutical industry within the preceding 5 years.

_____

4. Other interest which you consider, should be made know to the IMB:

_____

I, _____, do hereby declare on my honour that, to the best of my knowledge, the only direct or indirect interests I have in the pharmaceutical industry which are capable of affecting the objective discharge of my responsibilities to the Agency are those listed above.

I further declare that should it appear that I have or acquire additional interests which should be made know to the IMB, I shall forthwith declare them.

Done at: _____, on _____

_____

(signature)

- Includes the manufacture, importation or distribution of herbal, alternative and/or traditional medicinal product

Appendix 7 Confidentiality Agreement – Interested Organisations

CONFIDENTIALITY AGREEMENT

In discharging its statutory function the Irish Medicines Board deals with highly confidential matters, including information on patients' reactions to drugs and pharmaceutical* company formulations in medicines.

As an Interested Organisation being consulted as part of confidential work-in-progress, you are prohibited from disclosing any confidential information obtained from the Board. In addition, records/documentation must never be left in such a manner that unauthorised persons can obtain access to them.

I, , the chairperson of agree to be bound by this confidentiality agreement.

Signed: _____

Dated: _____

* Includes the manufacture, importation or distribution of herbal, alternative and/or traditional medicinal product

Appendix 8 Template for Product Information required for the Herbal Medicines Database

IMB HERBAL/TRADITIONAL PRODUCTS DATABASE INFORMATION TEMPLATE						
Manufacturer name & address	Distributor name & address	Product name	Latin Name and plant part	Common name	Weight/volume of ingredients	Health-medical claim/statement/s

Appendix 9 IMB Comments on the EU 'Provisions of a Directive on Traditional Medicinal Products'

The following is the Irish Medicines Board [IMB] response to the 'Provisions of a Directive on Traditional Medicinal Products' issued by the European Commission to each Member State for comment.

Chapter I

Definitions and Scope

Article 1

1. This is acceptable to the Irish Medicines Board.

2. The Irish Medicines Board recommends that a list of products [other than herbal medicinal products as defined in Article 1.1] that are either already on the market or likely to be on the market in Member States and are considered to be 'traditional' should be included in the scope of the new Directive. The Irish Medicines Board acknowledges that in composing this definitive list it is important to consider those products which do not necessarily have a traditional use in Ireland but which are used extensively in other Member States. This list should, however, be clearly defined and delineated. The provisions of Article 1.2 should therefore include **at least** the following:
   a.) fish oils and preparations thereof,
   b.) royal jelly and other insect products,
   c.) kelp and other traditionally used products of marine origin e.g. fish proteins,
   d.) acidobifidus and lactobacillus and preparations thereof.

3. The products outlined in Article 1.1 and Article 1.2 of this Directive should carry the same labelling requirements. In addition to a statement clearly indicating the 'traditional' status of these products, the caveat statement 'Not clinically proven' should be included on the label.

Article 2

1. This is acceptable to the Irish Medicines Board.

2. The Herbal Medicinal Products Working Party [HMPWP] definition is acceptable to the Irish Medicines Board:

   'Herbal drugs are mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually in dried form but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal drugs. Herbal drugs are precisely defined by the botanical name according to the binomial system (genus, species, variety and author)'

3. The HMPWP definition is acceptable to the Irish Medicines Board:

   'Herbal drug preparations are obtained by subjecting herbal drugs to treatments such as extraction, distillation, expression, fractionation, purification, concentration and fermentation. These include comminuted or powdered herbal drugs, tinctures, extracts, essential oils, expressed juices and processed exudates'

Chapter II

Placing on the Market

Article 3

1. Where herbal medicinal products have been registered under 65/65/EEC in the past but do not 'strictly speaking' meet the efficacy requirements of 65/65/EEC, these products could be offered the opportunity of 'traditional use' registration on a once off basis at the request of the product licence holder.

   Where herbal medicinal products comprise of herbal drugs or herbal drug preparations, which are considered 'Prescription only medicines', these should remain controlled under 65/65/EEC. However, herbal drugs or herbal drug preparations and herbal medicinal products currently considered 'prescription only' simply because of the absence of another suitable legislative location for them could be reviewed in light of this new Directive.

   This provision should not, however, prohibit a herbal medicinal product which meets the requirements of 65/65/EEC, being registered under 65/65/EEC regardless of other similar products being registered under this Directive or vice versa. The indication claims allowable under the two Directives would differ considerably.

2. It may be useful in this context to draw up a positive list of herbal drugs as per Article 5 of this Directive and the indications for which they can be licensed along the lines of the French 'Avis aux fabricant'. Positive lists should be drawn up on a national level with negative lists, as per Article 9 of this Directive, could be centrally produced. The Herbal Medicinal Products Working Party [HMPWP] of the European Medicines Evaluation Agency [EMEA] is an appropriate body to assume responsibility for this task.

3. Member States who do not wish to implement the new Directive, should by **one year** from adoption of the Directive, allow the use in its territory of herbal medicinal products registered in other Member States.

Article 4

1. This is acceptable to the Irish Medicines Board.

2. This is acceptable to the Irish Medicines Board.

3. a.) In the context of this Directive, Article 4.3 of Directive 65/65/EEC should read:

   'Qualitative and quantitative particulars of all constituents of the proprietary product in *both the common and Latin [binomial system including genus, species, variety and author as per the Index Kewensis] terminology,* ~~but excluding empirical chemical formulae~~, with mention of the international non-proprietary name recommended by the World Health organisation where it exists'

   b.) This is acceptable to the Irish Medicines Board.

   c.) It seems questionable whether evidence of equivalence dosage [point (iii)] can actually be provided for herbal medicinal products. If this information were to be considered 'additional' rather than 'binding proof' it may be useful guideline.

   Overall, the definition of tradition as time on the market, thirty years or otherwise, may not be appropriate as an inclusion criterion for this Directive. It is the opinion of the Irish Medicines Board that the definitions laid down in Article 1 of this Directive are more suitable as criteria for inclusion. The proof of traditional use over a defined

period of time should be additional information and should form the bases for any authorised label claim. Where evidence of traditional use is absent, e.g. in the case of a new indication for a herb or a new herb, the product should be registered under 65/65/EEC and full evidence of efficacy provided.

N.B. cf. comment on Article 4.4 below.

d.) This is acceptable to the Irish Medicines Board.

4. I refer to the comment made under Article 4.3 above. The provisions of Article 4.4 would then apply also to the label claim rather than the inclusion/exclusion of an herbal medicinal product from registration under the new Directive. A period of time which would be acceptable in addition to thirty years in either a.) a specific territory or territories outside the EEC, or b.) partly in one or more of the Member States, and partly in such a specified territory or territories, should be specified.

However, if the definition of 'traditional use' as thirty years on the market is to be acceptable, it is the opinion of the Irish Medicines Board that it should refer to the **herbal drug** and/or the **herbal drug preparation** and **not** the **herbal medicinal product** as this would seriously limit the number of products which would then be eligible for registration under the new Directive. The product being considered for licensing under the new Directive would only be allowed to make a 'traditional use' claim, where such use of the herbal drug/herbal drug preparation or combination [?] can be shown by reference to the time on the market.

5. Where a national positive list is available [cf. comment on Article 3.2 above], the regulatory agency of the Member State concerned may provide that where a product appears on such a list, an applicant need not provide the evidence specified in Article 4.3 b.) to d.) and Article 4.4.

6. The Irish Medicines Board acknowledges the fact that the SPC requirements under 65/65/EEC may be excessive for these products. However, the SPC should detail at least the following:

a.) Claimed 'indication',
b.) Dosage,
c.) Contra-indications,
d.) Special warnings and Special precautions for use,
e.) Interactions,
f.) Pregnancy and lactation,
g.) Effects on ability to drive and operate machinery,
h.) Undesirable Effects, and
i.) Overdose.

7. a.) This is acceptable to the Irish Medicines Board.

b.) The Irish Medicines Board feels that to allow a product to be marketed for a purpose other than that which has been traditionally proven is inappropriate and may lead to indication claims which are totally unsubstantiated either in tradition or otherwise. From the consumer point of view this would be both misleading and potentially unethical. Where a herb is indicated for a new indication, a full application under 65/65/EEC with evidence of efficacy would be desirable.

c.) The usefulness of a provision that allows a product to be marketed for use by a different route of administration to that which has been traditionally proven is questionable e.g. an herbal drug, herbal drug preparation or herbal medicinal product has been shown to be useful in the treatment of for example 'aiding restful sleep' when taken orally but the merit/logic of licensing it for topical use is unclear?

d.) Licensed use in another Member State should be acceptable as evidence of traditional use [cf. Article 4.3 c.) and Article 4.4].

Article 5

1. This is acceptable to the Irish Medicines Board.

2. a.) This is acceptable to the Irish Medicines Board.

   b.) The 'specified purposes' referred to in this paragraph should be limited to minor indications. The term 'minor indication' should be clearly defined, possibly as **an indication suitable for self-diagnosis and/or self-medication that does not normally require the intervention of a medical doctor.** A positive list of those minor indications acceptable under the new Directive could be drawn up at national level – cf. Article 3.2 and Article 4.5.

   c.) This is acceptable to the Irish Medicines Board.

   d.) This is acceptable to the Irish Medicines Board.

   e.) This is acceptable to the Irish Medicines Board.

3. This is acceptable to the Irish Medicines Board.

Article 6

1. This is acceptable to the Irish Medicines Board.

2. a.) This is acceptable to the Irish Medicines Board.

   b.) The relevant CPMP Notes for Guidance on the Quality of Medicinal Products that are appropriate for herbal medicinal products should be specified here.

   c.) The new EP monograph on Extracts is under review. The proposed changes to the current monograph are to be commented on by each Member State and should this result in an acceptable monograph it could then be considered as an acceptable reference for the new Directive.

3. According to this Directive, toxicological and pharmacological data are not required. As this is what Part 2 of the Annex to Directive 75/318/EEC relates it is unclear why it needs to be considered for 'medicinal products having simple presentation' or indeed any other products, which are covered under this Directive.

   Where a herbal tea is considered a herbal medicinal product, it is the opinion of the Irish Medicines Board that the SPC should contain the same information as all other herbal medicinal products [cf. Article 4.6].

Article 7

This is acceptable to the Irish Medicines Board.

Article 8

1. a.) This is acceptable to the Irish Medicines Board.

   b.) This is acceptable to the Irish Medicines Board.

c.) This is acceptable to the Irish Medicines Board.

d.) If a period of thirty years is to be accepted it should relate to herbal drug/herbal drug preparation and not to herbal medicinal product – cf. Articles 4.3 and 4.4.

e.) This is acceptable to the Irish Medicines Board.

f.) In the herbal context, 'essential similarity' is difficult to establish conclusively. However the Irish Medicines Board acknowledges then need to address the issue with regard to those products that are already licensed under 65/65/EEC. It may be appropriate to allow products already licensed under 65/65/EEC in certain Member States to retain their status quo in those countries, unless the applicant wishes to withdraw the product and reapply under this new Directive.

g.) This is acceptable to the Irish Medicines Board.

h.) This is acceptable to the Irish Medicines Board.

2. This is acceptable to the Irish Medicines Board.

3. This is acceptable to the Irish Medicines Board.

Article 9

1. A 'negative' list of herbal drugs is, in the opinion of the Irish Medicines Board, an important inclusion in the Directive. Such a list could be compiled by the HMPWP of the EMEA.

2. This is acceptable to the Irish Medicines Board.

Whether to adopt a 'positive' list as indicated in Article 5 of this Directive and/or a 'negative' list as proposed in this Article should be considered? As indicated in Article 3.2, a centrally produced 'negative' list and the option of producing national 'positive' lists would be optimal.

Article 10

1. A 'negative' list of therapeutic indications is, in the opinion of the Irish Medicines Board, an important inclusion in the Directive. As Article 9.1, such a list should be centrally produced and could be compiled by the HMPWP of the EMEA.

2. This is acceptable to the Irish Medicines Board.

Chapter III
Application of other Directives

Article 11

The application of the same testing criteria as outlined in Council Directive 65/65/EEC is imperative to ensure the same high quality in herbal medicinal products as expected for medicinal products generally. However, Article 8 of Directive 65/65/EEC refers to the following:

'Control methods employed by the manufacturer (analysis and assay of the constituents and the finished product, special tests, e.g. sterility tests, tests for the presence of pyrogenic substances, the presence of heavy metals, stability tests, biological and toxicity tests)'

It may be appropriate to emphasise the need to stringently test the starting material for microbial contamination in the case of herbal drug preparations and herbal medicinal products. Unlike conventional medicinal products, the herbal drug is the greatest potential source of contamination in herbals. In this context, Good Agricultural Practice [GAP - see Draft Proposal for Guidance on Good Agricultural Practice and Collection Practice for starting materials of Herbal Origin – EMEA/HMPWP/31/99] and Good Manufacturing Practice [GMP] should be adhered to.

Article 12

1. Directive 92/26/EEC refers to the classification for supply of medicinal products and divides them into:

   -medicinal products subject to prescription control,
   -medicinal products not subject to prescription control.

   It is the opinion of the Irish Medicines Board that 'prescription only' medicinal products should not be registered under this Directive as where concerns regarding either a.) the safety or b.) the potential for abuse exist or where the constituents are regulated under more stringent regulations, evidence of efficacy based upon reference to 'traditional use' is insufficient and the benefit relative to the documented risk is questionable. These products would be more effectively controlled under 65/65/EEC.

2. This is acceptable to the Irish Medicines Board.

3. a.) This is acceptable to the Irish Medicines Board.

   b.) This is acceptable to the Irish Medicines Board.

4. This is acceptable to the Irish Medicines Board.

5. This is acceptable to the Irish Medicines Board.

Chapter IV
Information sharing and final provisions

Article 13

This is acceptable to the Irish Medicines Board.

Article 14

1. This is acceptable to the Irish Medicines Board.

2. This is acceptable to the Irish Medicines Board.

With regard to specific provision for transitional arrangements, it is important that a significant transition period be allowed for those Member States where herbal medicinal products are currently 'unregulated'. In such instances the Member State could issue a 'product licence of right' to all products on the market at the time of introduction of the new Directive on the condition that the licence holder commit to applying for traditional use registration. Products introduced onto the market after the introduction of the Directive would have to apply through

the new Directive for a traditional use licence. Each Member State should provide a commitment to review all products already on the market within five years of introduction of the new Directive.

The Notice to Applicants and all relevant Guidelines e.g. GAP, GMP, GDP should be available to the applicants as soon as possible. The applicant would have to comply with the Directive and Guidelines within a specified period of time e.g. 3 years following introduction of the new Directive.

Appendix 10 IMB/SCHMP Comments on Draft 2 of the proposed EU 'Directive on Traditional Medicinal Products'

The following is the Irish Medicines Board [IMB] response to the 'Directive on Traditional Medicinal Products – Draft 2' issued by the Pharmaceutical Committee of the European Commission to each Member State on 5th April 2001 for comment.

Chapter I

Scope and Definitions

Article 1 – Scope of application

1. The Irish Medicines Board fully supports Article 1.1 but would like to seek clarification that the Annex to the Directive will be in place at the time of entry into force.

2. In principle the Irish Medicines Board accepts this Article. However, the use of the term 'can be' in the first sentence raises the question whether a.) it is products already licensed under 65/65/EEC that cannot now become registered under this Directive or b.) it is also intended to cover products that in the future apply for authorisation under 65/65/EEC. This needs to be clarified. It may be more appropriate to replace the word 'can' with the word 'should'.

   In addition the Irish Medicines Board would like to raise the issue of anthroposophic medicines as these are not covered under either 65/65/EEC or 92/73/EEC. However, they are not likely to be covered under this Directive, as they are more akin to homeopathic medicines than to herbal or traditional medicines, although many could provide evidence of 30 years use.

   Finally, many of the ethnic traditional medicines contain substances of animal and mineral origin. Will these be covered under this Directive? If not, this may unfairly discriminate against these products.

3. It is the opinion of the Irish Medicines Board that this provision should also apply to 'qualified medical herbalists'. However, this term would then need to be defined in the context of this Directive.

Article 2 - Definitions

1. This is acceptable to the Irish Medicines Board.

2. The Herbal Medicinal Products Working Party [HMPWP] of the European Medicines Evaluation Agency [EMEA] have adopted the term 'Herbal Drug' for the suggested 'Herbal Substance'. The Irish Medicines Board would support the Pharmaceutical Committee suggestion in light of the fact that 'substance' is defined in 65/65/EEC. However, in the interest of consistency, a common approach to terminology should be adopted.

   The Irish Medicines Board would like clarification on the position with regard to combinations of herbal substances with other non-herbal substances. If these can prove a tradition of use are they included? As there are many of these products currently available on the market, they should be considered here.

3. The Irish Medicines Board would again support the Pharmaceutical Committees terminology i.e. 'Herbal Preparation' but would also like this to be consistent across all European Agencies i.e. HMPWP terminology is 'Herbal Drug Preparation'.

In addition the Irish Medicines Board requests that, for completeness, 'fixed oils' should be included in the final sentence of the proposed definition of 'Herbal preparations'.

Chapter II

Registration

Article 3 – Application

1. This is acceptable to the Irish Medicines Board.

2. This is acceptable to the Irish Medicines Board.

3. a.) The exclusion of 'the results of pharmacological tests' requirements as outlined in paragraph 4 of Article 4(a) of 65/65/EEC may not be completely appropriate as paragraphs 5 and 6 of the same Article request information on 'therapeutic indications, contra-indications, side-effects and posology'. It may be more appropriate to develop new requirements for 'traditional medicinal products' in the context of the present Directive.

In the context of this Directive Article 4.3 of Council Directive 65/65/EEC should read:

> 'Qualitative and quantitative particulars of all constituents of the proprietary product in *both the common and Latin [binomial system including genus, species, variety and author as per the Index Kewensis] terminology*, ~~but excluding empirical chemical formulae~~, with mention of the international non-proprietary name recommended by the World Health organisation where it exists'

b.) This is acceptable to the Irish Medicines Board.

c.) As stated previously, the Irish Medicines Board is of the opinion that if the definition of 'traditional use' as thirty years on the market is to be acceptable, it should refer to the **herbal substance** and/or the **herbal preparation** and **not** the **herbal medicinal product** as this would seriously limit the number of products which would then be eligible for registration under the new Directive. A product would then only be considered for licensing under the new Directive, where such use of the herbal substance/herbal preparation or combination could be shown by reference to the time on the market.

Article 3.3(c)(i) should more precisely define the 'same ingredients' in terms of plant/plant part etc.

It is the opinion of the Irish Medicines Board that the term 'purpose' should, more appropriately, read 'use' in Article 3.3(c)(ii).

The Irish Medicines Board would like clarification on whether the requirements of Article 3.3 (c) (iii) would prohibit the registration of standardised extracts that cannot demonstrate 30 years of use? If this is the case, it may lead to inconsistency in the registration/authorisation of standardised herbal medicinal products and require that some but not all must, by default, be authorised under Council Directive 65/65/EEC.

d.) It is the opinion of the Irish Medicines Board that a bibliographic review of the safety data will always be required and therefore would request that the second sentence be deleted.

It is unclear from this Article whether post-marketing surveillance data and PSUR reports will form part of the requirements for application. It is the opinion of the Irish Medicines Board that these data are valuable sources of both safety and efficacy information and should definitely form part of the 'bibliographic review' process.

4. The Irish Medicines Board would be happy to see the requirement of '15 years' be reduced to '10 years' in order to facilitate the inclusion of the large and growing number of ethnic medicines on the European market.

5. This is acceptable to the Irish Medicines Board.

Article 4 – Dossier on testing

1. This is acceptable to the Irish Medicines Board.

2. This is acceptable to the Irish Medicines Board.

3. The Irish Medicines Board fully supports Article 4.3 which allows for a simplified dossier to submitted for herbal teas and herbal tinctures. It may also be appropriate to include herbal juices in this Article.

The final sentence should read 'Article 14' and not 'Article 16' as in the current text.

Article 5 – Allowed substances/indications

The Irish Medicines Board would support the development of a centralised 'positive list' for herbal substances and associated accepted medical indications. It is suggested that the 'Avis aux Fabricants' may provide valuable guidance in this context. In this context we would prefer to see the text read 'shall be' rather than 'may be' as in the current text. However, it is our assumption that this list would not be binding and could be changed or added to as additional information became available.

See also comments on Article 8.

Article 6 – registration by other Member States

It is unclear what is meant by Article 6 in practice. Is it envisaged than these products will ultimately be authorised through a mutual recognition procedure?

Article 7 – Refusal of registration

The use of the term 'not plausible' in Article 7(d) is of concern to the Irish Medicines Board as it is both vague and subjective. It may be more appropriate to use the term 'not acceptable'

The Irish Medicines Board fully supports the exclusion of medicinal products subject to prescription control as indication in Article 7(e). However, it may be appropriate to include a provision for 'qualified medical herbalists' to retain access to these herbal substances/preparations/medicinal products.

Article 7(g) should read 'this Directive' rather than 'a Directive' as in the current text.

Article 7(h) might, more appropriately read 'pharmaceutical quality <u>is</u> not <u>satisfactorily</u> demonstrated'. It may also be necessary to define 'pharmaceutical quality in the context of this Directive.

In accordance with Article 4 of 65/65/EEC, an applicant must provide documentary evidence that the site of manufacture within the EEA is licensed. As manufacturing sites outside the EEA cannot be licensed, it may be appropriate to include a provision for refusal of registration if such a site is not compliant with the EEA Good Manufacturing Practice [GMP] guidelines.

Article 8 – List with specific traditional medicinal products

This is a significant departure from the original proposal and it is unclear what the purpose of a second 'positive list' [cf. Article 5] would be? It is the opinion of the Irish Medicines Board that such a list of 'products', while facilitating harmonisation, would be too restrictive at a national level. The need for such a list is questionable in light of the provisions of Article 5.

It is of particular concern that such a list of 'products' would be binding on each Member State and would devolve responsibility for product assessment and decision making from each MS [cf. 'exclusions' as indicated in Article 8.3].

The distinction between 'product' and 'substance' is critical in this context and it is our assumption that the purpose of a 'positive list' of substances/indications' [as per Article 5] it would be to facilitate registration at MS level but not to centrally determine what can and cannot be registered?

Article 9 – Adaptation to new monographs

This is acceptable to the Irish Medicines Board.

Chapter III
Application of other Directives

Article 10 – General reference

In accordance with Article 7 of EU Council Directive 65/65/EEC, an application would have to be assessed within 120 days of submission. While this may be feasible in the long term, it would not be appropriate in the first instance when the number of products to be assessed is likely to be very large particularly in those MS that do not current have a licensing system for these products.

It is the opinion of the Irish Medicines Board that the provisions of 75/319/EEC should also apply to third country imports of traditional medicinal products, although it is acknowledged that a guideline for the implementation of such a provision would be necessary. Implicit in such a provision is the extension of the role of the Competent Authority of individual MS to inspect a manufacturing site in a non-EEA country.

The Irish Medicines Board would also suggest a reference to EU Council Directive 91/356/EEC, which details the requirements for Good Manufacturing Practice, in this Article.

Article 11 – Labelling and package leaflet

1. Article 11.1(b) should read 'doctor or qualified practitioner'.

2. This is acceptable to the Irish Medicines Board.

Article 12 - Advertising

This is acceptable to the Irish Medicines Board.

Chapter IV
Final provisions

Article 13 – Information about refusal of registration

It is the opinion of the Irish Medicines Board that information regarding refusal of registration should be **automatically** provided to the Commission and other MS competent authorities.

Article 14 - Committee

The Irish Medicines Board fully supports the establishment of an EMEA committee that will exclusively deal with herbal and traditional medicinal products. The remit of this committee, as outlined in Article 14.3, represents a significant move forward in successfully implementing EU Council Directive 1999/83/EC, an important instrument in licensing of herbal and other traditional medicinal products that will not qualify for registration under this current Directive.

Article 15 – Implementation

1. The Irish Medicines Board would support a three year implementation period in the context of the provisions of paragraphs 2 and 3 of this Article.

2. This is acceptable to the Irish Medicines Board.

3. This is acceptable to the Irish Medicines Board.

Appendix 11 SOP for Refusal of an Application for a Product Registration

IRISH MEDICINES BOARD	ADMINISTRATIVE PROCEDURES		
Procedure Type SOP	**Procedure No.**	**Revision**	**Page 1 of 10**
TITLE: Standard Operating Procedure for Rejection of Applications for Product Registration for Traditional Medicinal Products for Human Use.			
Written by **Date**	**Approved by** **Date**	**Effective Date**	

1. SCOPE

This SOP describes the official procedure to be followed when applications for registration are recommended for rejection.

2. INTRODUCTION

This procedure applies to any application for a product registration through National procedures.

3. EXHIBITS

Exhibit 1 - Flow Chart
Exhibit 2 - Rejection Criteria
Exhibit 3 - Format of rejection proposal
Exhibit 4 - Recommendation to reject, letter format.
Exhibit 5 - Rejection, letter format.

4. REFERENCES

4.1 Irish Medicines Board Act 1995.
4.2 Medical Preparations (Licensing and Sale) Regulation, 1996 (S.I. 43 of 1996).
4.3 Regulations for an interim national licensing scheme for traditional medicinal products – as per this proposal.

5. REVISION HISTORY

Revision 1, 15th October 2001.

6. INSTRUCTION

6.1 Rejection Procedure

(See Exhibit 1 - Flow Chart of Rejection Procedure)

6.1.1 Defects identified during the course of an assessment are relayed to the applicant. Reasonable opportunity is given to the applicant to reply.

6.1.2 Where it is not possible to resolve the deficiencies and in the opinion of the assessor **(and taking into account any consultative expert advice obtained*)**, a fundamental objection in terms of quality, safety or traditional use/indication claim remains (Exhibit 2), the products are scheduled for rejection in consultation with the Head of the Traditional Medicinal Products Unit (cf. Article 14 of the proposed interim national regulations – Ref. 4.3).

6.1.3 The company is informed by the assessor that it is intended to recommend the application for rejection.

6.1.4 The application is put forward for rejection to the next available meeting of the Executive Committee. The rejection should be presented in the standard format (Exhibit 3) showing the name of the company, the traditional registration number, the name of the product, the active ingredients and an indication of the reason for rejection. The details of deficiencies leading to recommendation for rejection should be outlined. The rejection proposal should be signed by the assessor and the head of the unit.

6.1.5 At the meeting of the Executive Committee the Unit Head outlines the reasons for recommendation for rejection and the opinion of the Executive Committee is adopted and documented by the recording secretary. If the proposal is endorsed, the signature page is signed on behalf of the Executive Committee.

*** NOTE: Expert advice includes the opinion of the Sub-Committee on Traditional Medicinal Products (cf. Article 15 of the proposed interim national licensing scheme – Ref. 4.3).**

6.1.6 The company is advised by standard letter (Exhibit 4) of the intention to present the application for rejection to the Advisory Committee. The company will be advised that it has 30 days from the date of the letter to submit any comments. Any resulting comments will be reviewed by the assessor(s), the Unit Head and the Executive Committee. If these do not resolve the underlying reasons for rejection, the proposal for rejection will stand. Rejected applications must then be referred to the Advisory Committee for Human Medicines*.

6.1.7 The proposal to reject is scheduled for presentation and review at a meeting of the Advisory Committee.

6.1.8 If the Advisory Committee agrees with the recommendation of the Executive Committee then a recommendation to reject the application will be made and the signature page signed on behalf of the Advisory Committee. If the Committee disagrees with the recommendation of the Executive Committee, then it may refer the matter back to the Executive Committee or institute its own review procedure or refer the matter to the Board for review.

6.1.9 Recommendations for rejection by the Advisory Committee will be notified to the Board. These will normally be presented to the next scheduled Board meeting.

Following the agreement of a rejection by the Board, the applicant will be notified by way of a letter (Exhibit 5).

6.1.10 Following rejection by the Board, any resulting appeal by the applicant must be made to the Board.

6.1.11 The applicant has the right to withdraw the application at any stage in the rejection process.

*** NOTE: The chairperson of the Sub-Committee on Traditional Medicinal Products will be a member of the Advisory Committee on Human Medicines (cf. Article 15 of the proposed interim national licensing scheme – Ref. 4.3).**

Exhibit 1 - Flow Chart of Rejection Procedure

Applicant informed of defects and given opportunity to respond.

⇓

If defects not resolved and with agreement of Head of Traditional Medicines Unit [**and following review of expert advice including the opinion of the Sub-Committee on Traditional Medicinal Products**], the assessor informs the applicant that the product will be recommended for rejection.

⇓

Recommendation for rejection presented to the Executive Committee.

⇓

If Executive Committee adopts the recommendation, the applicant is informed of the intention to present the application to the Advisory Committee. The applicant is given 30 days to comment.

⇓

Any comments received are reviewed by the Executive Committee and at the discretion of the relevant department head, by the assessor. If defects are not resolved, the recommendation for rejection is presented to the Advisory Committee.

⇓

If adopted by the Advisory Committee, the recommendation for rejection is presented to the Board.

⇓

If the Board adopts the recommendation, the applicant is notified of the rejection.

Note: Any appeal following rejection must be made to the Board.

Exhibit 2 - Rejection Criteria*

1. Where the application is found to be in breach of a requirement in National legislation.

2. Where the application is in breach of a National or European labelling or package leaflet regulations.

3. Where the applicant fails to comply with a recommendation given in a guideline which is of fundamental importance to the quality, safety or traditional use/indication claim of that product, and where no justification for an alternative approach is made.

4. Failure to supply a fundamental part of the dossier or adequate safety/traditional use/claim data.

5. Where the applicant fails to reply to questions within an acceptable time frame. For review products this time should not exceed 3 months.

*** see Refusal of a Product Registration - Article 11 of the proposed interim national licensing scheme (Ref. 4.3).**

Exhibit 3

Irish Medicines Board

Proposal For Rejection

Product Name:

Traditional Registration Number:

Company Name:

Review by Executive Committee:

_____ _____

Signed for and on behalf of Executive Committee **Date**

Review by Advisory Committee:

_____ _____

Signed for and on behalf of Advisory Committee **Date**

Review by Irish Medicines Board:

_____ _____

Signed for and on behalf of the Board **Date**

Exhibit 3 (Cont/d)

Irish Medicines Board

Proposal For Rejection

Company Name:

Submission Prepared By:

Traditional Registration Number:

Product Name:

Active Ingredient(s) (i.e. herbal substance/preparation or non-herbal substance – see Article 1 and 2 of the proposed interim national licensing scheme – Ref. 4.3):

Rejection Proposal Prepared By:

Reason For Rejection:

Here list the reason or reasons for rejection. Give details of the deficiencies, any relevant questions to and responses from the applicant with a chronology, if appropriate. Attach copies of any relevant correspondence.

Exhibit 3 (Cont/d)

Conclusions:

Give a brief summarising and concluding statement which contains the main reason(s) for rejection.

Grounds For Rejection:

List any relevant national regulations or European Directives, which form the basis for the rejection proposal.

Assessor making proposal:

_____ _____

Signature Date

Head of Traditional Medicines Unit:

_____ _____

Signature Date

Exhibit 4 - Notification of Intention To Recommend Rejection

To:

Re:

Dear Sirs,

Your application for registration of the above product was reviewed by the Executive Committee at its meeting of . I am to inform you that it is their decision to recommend to the Advisory Committee for Human Medicines of the Irish Medicines Board that the application be rejected on the grounds of failure to comply with . You are invited to submit any comments that you may have within 30 days of the date of this letter.

Yours faithfully,

Exhibit 5 - Rejection Letter

To:

Re:

Dear Sirs,

The Irish Medicines Board, at its meeting on the , rejected the above application for product registration on the basis of failure to satisfy the Board's requirements as specified in

Yours faithfully,