

Traditional Herbal Medicinal Products

Registration Dossier Requirements
November 2004



Registration Dossier Requirements

- ▶ Aims of MHRA

- ▶▶ to provide early guidance to potential applicants

- ▶▶ provide effective, efficient service to industry

- ▶▶ offer timely regulatory and scientific advice

- ▶▶ www.mhra.gov.uk

Registration Dossier Requirements

- ▶ Strategy for advising potential applicants two-pronged
 - ▶▶ seminars
 - ▶▶ regulatory/scientific advice meetings
- ▶ Pre-application Notifications
 - ▶▶ >35 potential applicants
 - ▶▶ >500 products
 - ▶▶ meetings underway with potential applicants

Registration Dossier Requirements

Aims and objectives of this seminar

- ▶ to provide an introduction and early guidance to potential applicants on the registration dossier
- ▶ to take a look at the dossier from 'top to toe'
- ▶ to focus on herbal products

Challenges - because participants have widely differing experience of regulation

Registration Dossier Requirements

Future seminars

- ▶ more specialised sessions
 - ▶▶ eg. Herbal CTD, quality, stability testing
 - ▶▶ combinations with vitamins/minerals
 - ▶▶ writing Safety Expert Report,
 - ▶▶ specific traditions e.g. TCM, Ayurvedic
 - ▶▶ variations and renewals
- ▶ welcome views from participants

Traditional Herbal Medicinal Products

Registration Dossier Requirements
November 2004



Traditional Herbal Medicinal Products

Requirements for THMPD

Maureen Riach

Requirements for THMPD

- ▶ Overview of the THMPD requirements
- ▶ Participants have widely differing experiences of regulation
- ▶ Pre-application notifications showed some confusion about the requirements

Requirements for THMPD

Pre-application notifications:

- ▶ some products contained no herbal ingredients
- ▶ some products contained conventional drug substances
- ▶ some products contained non-herbal active ingredients eg. menthol, camphor, glucosamine
- ▶ one product contained an *Aristolochia* species
- ▶ many products had indications unsuitable for self-medication

Definitinos and Terminology

Herbal medicinal product defined in THMPD as

“any medicinal product exclusively 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”

Definitinos and Terminology

- ▶ Herbal substances are defined as
“mainly whole, fragmented or cut, plants, parts of plants, algae, fungi, lichen in an unprocessed state, usually 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 scientific name according to the binomial system.”
- ▶ **‘herbal substance’** equivalent to **‘herbal drug’** in EP

Definitinos and Terminology

- ▶ Herbal preparations are defined as:
“obtained by subjecting herbal drugs to treatments such as extraction, distillation, expression, fractionation, purifications, concentration or fermentation. These include comminuted or powdered herbal drugs, tinctures, extracts, essential oils, expressed juices and processed exudates.”
- ▶ **‘herbal preparation’** equivalent to **‘herbal drug preparation’** in EP

Traditional Herbal Medicinal Products Directive 2004/24 EC

- ▶ THMPD adopted 31st March 2004
- ▶ amends Directive 2001/83/EC on the Community Code relating to Medicinal Products for Human Use
- ▶ Informal Consolidated version of Directive 2001/83/EC incorporating amendments by 2004/24/EC and 2004/27 is available

http://pharmacos.eudra.org/F2/eudralex/vol-1/CONSUL_2004/Human%20code.pdf

Requirements for THMPD

- ▶ Member States must implement the THMPD Directive and establish a registration scheme by 30th October 2005
- ▶ Article 2(2) of the THMPD provides that where traditional herbal medicinal products were already on the market when THMPD came into force Member States may allow a Transitional Period of up to 7 years
- ▶ MHRA's current intention is to allow the transitional period to run until 2011 in the UK

Requirements for THMPD

Article 16 a

Establishes a simplified registration procedure for herbal medicinal products for human use which fulfil all of the following criteria:

- ▶ indications and composition are suitable for use without supervision of a medical practitioner
- ▶ specified strength and posology
- ▶ oral, external and/or inhalation only
- ▶ evidence of medicinal use (30 years or 15 + 15)
- ▶ traditional use shows not harmful, plausible

Requirements for THMPD

- ▶ Vitamins/minerals may be added provided that their action is ancillary to that of the herbal active ingredients regarding the specified claimed indication(s)
- ▶ Product is not eligible for THMPD if it satisfies the criteria for:
 - ▶▶ marketing authorisation (Article 6)
 - ▶▶ homeopathic registration (Article 14)

Requirements for THMPD

Article 16b

- ▶ Applicant must be established in EU
- ▶ Application must be submitted to the competent authority of the Member State concerned

Requirements for THMPD

Article 16c: Application must contain

- ▶ details of applicant/manufacture
- ▶ name of the product
- ▶ qualitative and quantitative composition
- ▶ method of manufacture
- ▶ therapeutic indications, contra-indications, adverse reactions
- ▶ posology, pharmaceutical form, method and route of administration
- ▶ shelf-life and storage conditions

Requirements for THMPD

Article 16c contd:

- ▶ description of control methods
- ▶ results of pharmaceutical tests (physico-chemical, biological, microbiological)
- ▶ Summary of Product Characteristics (SPC)
- ▶ authorisation of the manufacturer (GMP)
- ▶ if combination not sufficiently known, data on individual active ingredients also
- ▶ any previous authorisations

Requirements for THMPD

Article 16c contd:

- ▶ bibliographic or expert evidence of product on market for 30 years including 15 years in the Community
- ▶ bibliographic review of safety plus Expert Report
- ▶ safety data where requested by MS
- ▶ evidence of use may be based on similar product (same actives, strength, posology) even where product has not been authorised
- ▶ or where number/quantity of ingredients has been reduced during the 30 year period

Requirements for THMPD

Article 16c contd:

- ▶ If product has <15 years use in EU but otherwise meets requirements can refer to Herbal Medicinal Products Committee (EMEA)

Requirements for THMPD

Article 16d

- ▶ Mutual Recognition shall apply to registrations if covered by a Community Herbal Monograph or
- ▶ The herbal ingredients are on the HMPC List
- ▶ MS have to take account of registrations granted by another MS

Requirements for THMPD

Article 16e:

The application shall be refused if it does not satisfy Articles 16a, 16b or 16c or if following not fulfilled:

- ▶ qualitative/quantitative composition not as declared
- ▶ therapeutic indications do not comply with 16a
- ▶ product is harmful under normal conditions of use
- ▶ data on traditional use insufficient/implausible
- ▶ pharmaceutical quality is not demonstrated

Requirements for THMPD

Article 16f

- ▶ The HMPC shall set up a list of herbal substances with indications, strength, route of administration
- ▶ if ingredients are on the list - evidence of traditional use, bibliographic review of safety do not need to be provided
- ▶ if ingredient removed from the list than registrations shall be revoked unless data provided within 3 months

Requirements for THMPD

Article 16g:

- ▶ states that all other legislation applying to medicinal products, their manufacture, advertising and sale shall also apply to traditional herbal medicinal products
- ▶ sets out specific requirements for labels, package leaflet and advertisements

Requirements for THMPD

Article 16h

- ▶ establishes Herbal Medicinal Products Committee (HMPC) as part of the EMEA
- ▶ tasks include preparing:
 - ▶▶ list of herbal substances, preparations and combinations
 - ▶▶ community monographs
 - ▶▶ assess evidence if traditional use < 15 years in EU

Requirements for THMPD

Article 16i

- ▶ by 30th April 2007 the Commission shall submit a report to the European Parliament and the Council concerning possible extension of registration to other categories of medicinal products

Requirements for THMPD

Points to consider:

- ▶ does your product fulfil the Requirements for THMPD?
- ▶ do you need to register?
- ▶ if the answer to both these questions is YES
- ▶ when do you need to register?
- ▶ does the transitional period apply to your product?

Requirements for THMPD

- ▶ if you plan to register within the first two years of the operation, have you notified MHRA using the voluntary PAN scheme?
- ▶ if not - why not?!
- ▶ don't miss your opportunity for regulatory/scientific advice
- ▶ if you are unsure about any aspects better to seek advice

Traditional Herbal Medicinal Products

Overview of the THMPD Dossier

Sue Harris

Preparing THMPD Dossiers

Getting started:

- ▶ decide on the formulation
- ▶ do you want to make any changes?
- ▶ if so – make the changes now
- ▶ define any overages/ ranges
- ▶ define the pack size and packaging materials
- ▶ assemble the documents/ guidance notes etc

THMPD Dossiers

Presentation and Format

- ▶ no specific guidance available to date on presentation/ format of THMPD dossiers
- ▶ Commission/ HMPC may produce guidance
- ▶ for marketing authorisations - 'Notice to Applicants'
- ▶ Article 16c 2001/83/EC as amended - states Annex I shall apply to the particulars/documents
- ▶ Annex I provides some guidance on presentation/ technical information
- ▶ will be CTD format

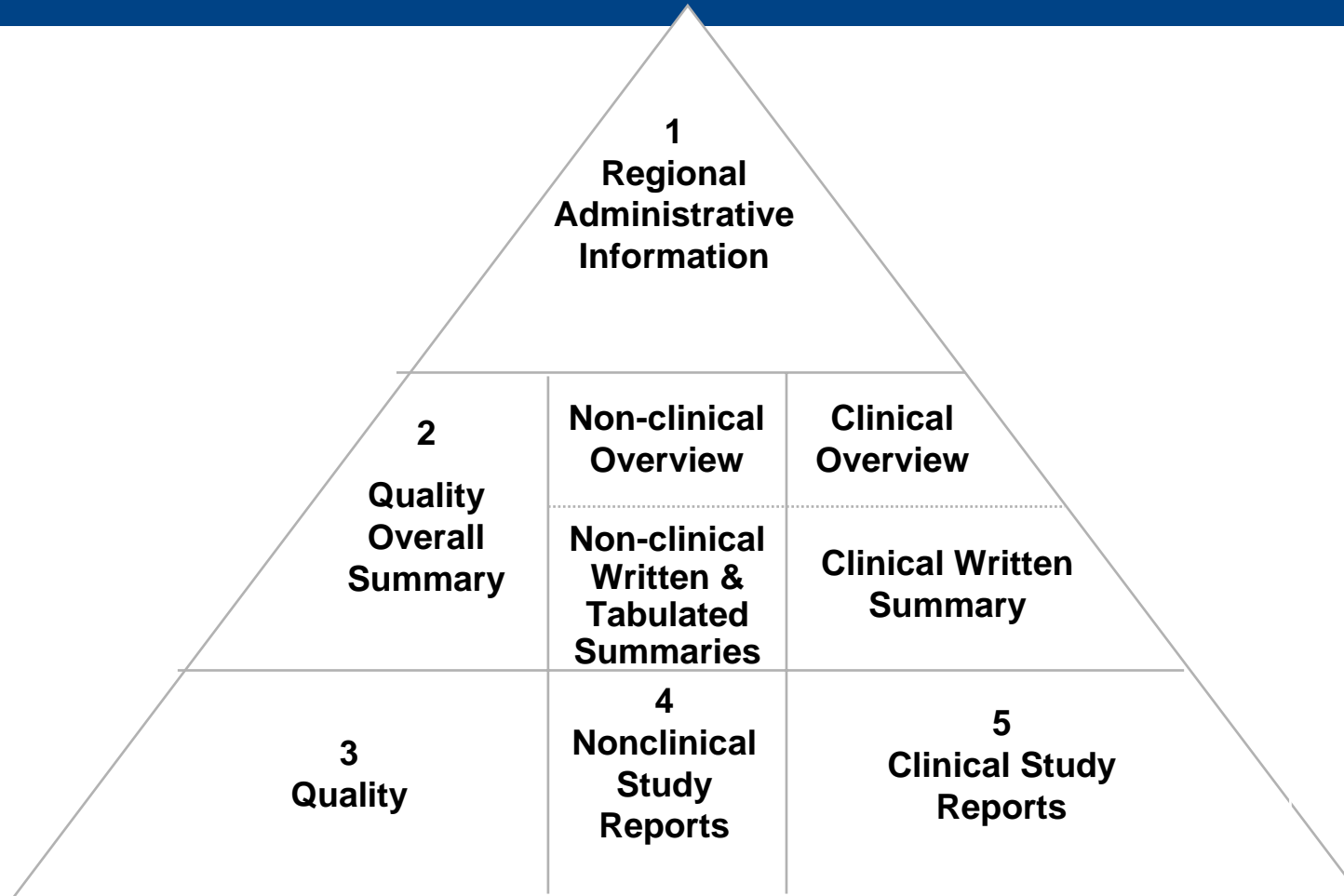
THMPD Dossiers Presentation and Format

- ▶ Common Technical Document (CTD)
- ▶ <http://pharmacos.eudra.org/F2/eudralex/vol-2/home.html>
- ▶ a common harmonised FORMAT for applications for preparing marketing authorisations in the three ICH regions of the EU, USA and Japan.
i.e. a TEMPLATE for presenting the data
- ▶ CTD basically an index
- ▶ with some guidance about what goes where
- ▶ detailed requirements set out in guidelines

THMPD Dossiers Presentation and Format

- ▶ Notice to Applicants and Annex I
 - ▶▶ special guidance on herbal medicinal products
 - ▶▶ Herbal 'CTD' uses same headings
 - ▶▶ some guidance on what goes where for herbal products
- ▶ CTD is organised into five modules

Diagrammatic Representation of CTD



MA Dossier Requirements

Common Technical Document (CTD)

- ▶ Module 1: Administrative information
- ▶ Module 2: CTD Summaries
- ▶ Module 3: Quality
- ▶ Module 4: Non-clinical Study Reports
- ▶ Module 5: Clinical Study Reports

THMPD Dossiers

Common Technical Document (CTD)

- ▶ Module 1: Administrative information
- ▶ Module 2: CTD Summaries
- ▶ Module 3: Quality
- ▶ Module 4: bibliographic review of safety*
- ▶ Module 5: traditional use evidence*

* UK guidance at this stage

THMPD Dossiers Presentation

General guidance

- ▶ display of information - unambiguous, transparent
- ▶ leave sufficient margins for binding
- ▶ margins for text and tables
- ▶ preferred font Times New Roman 12-point
- ▶ acronyms and abbreviations defined when first used

THMPD Dossier

Module 1: Administrative Data

- ▶ 1.1 Comprehensive Table of Contents
- ▶ 1.2 Application form
- ▶ 1.3 Summary of Product Characteristics (SPC),
Labelling and Package Leaflet
 - » 1.3.1 SPC
 - » 1.3.2 Labelling
 - » 1.3.3 Patient information leaflet (PIL)
 - » 1.3.4 Mock-ups and specimens
- ▶ 1.4 Information about the Experts (CV)
- ▶ 1.5 Environmental risk assessment

THMPD Dossier

Module 2: CTD Summaries

- ▶ 2.1 CTD Table of Contents
- ▶ 2.2 Introduction
- ▶ 2.3 Quality Overall Summary(QOS) - Introduction
 - ▶▶ 2.3.S QOS - drug substance
 - ▶▶ 2.3.P QOS - drug product
 - ▶▶ 2.3.A QOS - Appendices
 - ▶▶ 2.3.R QOS - Regional Information
- ▶ 2.4 Expert Report on safety
- ▶ 2.5 Clinical Expert Report (?) - seeking advice on this

THMPD Dossier

Module 3: Quality

- ▶ 3.1 Module 3 Table of Contents
- ▶ 3.2 Body of Data
- ▶ 3.3 Literature references

THMPD Dossier

Module 4: Safety

- ▶ 4.1 Module 4 Table of Contents
- ▶ 4.2 Bibliographic review
- ▶ 4.3 Literature references

THMPD Dossier

Module 5: Traditional Use Evidence

- ▶ 5.1 Module 5 Table of Contents
- ▶ 5.2 Traditional use evidence
- ▶ 5.3 Literature references

THMPD Dossier

Module 3: Quality

- ▶ **3.1 Table of Contents**
- ▶ **3.2.S Drug Substance**
- ▶ **3.2.S.1 General Properties**
 - ▶▶ 3.2.S.1.1 Nomenclature
 - ▶▶ 3.2.S.1.2 Structure
 - ▶▶ 3.2.S.1.3 General Properties

THMPD Dossier

Module 3: Quality

- ▶ 3.2.S.2 **Manufacture**
 - ▶▶ 3.2.S.2.1 Manufacturer(s)
 - ▶▶ 3.2.S.2.2 Description of Manufacturing Process and Process Controls
 - ▶▶ 3.2.S.2.3 Control of Materials
 - ▶▶ 3.2.S.2.4 Controls of Critical Steps and Intermediates
 - ▶▶ 3.2.S.2.5 Process Validation and/or Evaluation
 - ▶▶ 3.2.S.2.6 Manufacturing Process Development

THMPD Dossier

Module 3: Quality

- ▶ 3.2.S.3 **Characterisation**
 - ▶▶ 3.2.S.3.1 Elucidation of Structure and other Characteristics
 - ▶▶ 3.2.S.3.2 Impurities
- ▶ 3.2.S.4 **Control of Drug Substance**
 - ▶▶ 3.2.S.4.1 Specification
 - ▶▶ 3.2.S.4.2 Analytical Procedures
 - ▶▶ 3.2.S.4.3 Validation of Analytical Procedures
 - ▶▶ 3.2.S.4.4 Batch Analyses
 - ▶▶ 3.2.S.4.5 Justification of Specification

THMPD Dossier

Module 3: Quality

- ▶ 3.2.S.5 Reference Standards or Materials
- ▶ 3.2.S.6 Container Closure System
- ▶ 3.2.S.7 Stability
 - ▶▶ 3.2.S.7.1 Stability Summary and Conclusions
 - ▶▶ 3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment
 - ▶▶ 3.2.S.7.3 Stability Data

THMPD Dossier

Module 3: Quality

- ▶ 3.2.P Drug Product
- ▶ 3.2.P.1 Description and Composition of the Drug Product
- ▶ 3.2.P.2 Pharmaceutical Development
 - ▶▶ 3.2.P.2.1 Components of the drug product
 - » 3.2.P.2.1.1 Drug substance
 - » 3.2.P.2.1.2 Excipients

THMPD Dossier

Module 3: Quality

- ▶▶ 3.2.P.2.2 Drug Product
 - » 3.2.P.2.2.1 Formulation development
 - » 3.2.P.2.2.2 Overages
 - » 3.2.P.2.2.3 Physicochemical and biological properties
- ▶▶ 3.2.P.2.3 Manufacturing process development
- ▶▶ 3.2.P.2.4 Container closure system
- ▶▶ 3.2.P.2.5 Microbiological attributes
- ▶▶ 3.2.P.2.6 Compatibility

THMPD Dossier

Module 3: Quality

- ▶ 3.2.P.3 **Manufacture**
 - ▶▶ 3.2.P.3.1 Manufacturer(s)
 - ▶▶ 3.2.P.3.2 Batch formula
 - ▶▶ 3.2.P.3.3 Description of manufacturing process and process Controls
 - ▶▶ 3.2.P.3.4 Controls of critical steps and intermediates
 - ▶▶ 3.2.P.3.5 Process validation and/or evaluation

THMPD Dossier

Module 3: Quality

- ▶ 3.2.P.4 Control of Excipients
 - ▶▶ 3.2.P.4.1 Specifications
 - ▶▶ 3.2.P.4.2 Analytical procedures
 - ▶▶ 3.2.P.4.3 Validation of analytical procedures
 - ▶▶ 3.2.P.4.4 Justification of specifications
 - ▶▶ 3.2.P.4.5 Excipients of human or animal origin
 - ▶▶ 3.2.P.4.6 Novel excipients

THMPD Dossier

Module 3: Quality

- ▶ 3.2.P.5 Control of Drug Product
 - ▶▶ 3.2.P.5.1 Specification(s)
 - ▶▶ 3.2.P.5.2 Analytical procedures
 - ▶▶ 3.2.P.5.3 Validation of analytical procedures
 - ▶▶ 3.2.P.5.4 Batch analysis
 - ▶▶ 3.2.P.5.5 Characterisation of impurities
 - ▶▶ 3.2.P.5.6 Justification of specification(s)

THMPD Dossier

Module 3: Quality

- ▶ 3.2.P.6 Reference Standards or Materials
- ▶ 3.2.P.7 Container Closure System
- ▶ 3.2.P.8 Stability
 - ▶▶ 3.2.P.8.1 Stability Summary and Conclusion
 - ▶▶ 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment
 - ▶▶ 3.2.P.8.3 Stability Data

THMPD Dossier

Module 3: Quality

▶ 3.2.R Regional Information

- ▶▶ Process Validation Scheme for the drug product
- ▶▶ Certificate(s) of Suitability
- ▶▶ Medicinal products containing or using in the manufacturing process materials of animal and/or human origin (Tables A, B, C).

▶ 3.3 Literature References

Overview of The THMPD Dossier

- ▶ HMPC has been asked to provide guidance on Presentation and Format
- ▶ we will keep potential applicants informed of any forthcoming information via MHRA web-site
- ▶ applicants should familiarise themselves with CTD
- ▶ look at general CTD guidance (NTA and Annex I)
- ▶ look at herbal CTD guidance (NTA and Annex I)

Traditional Herbal Medicinal Products

Application Form

Sue Harris

THMPD Application Form

Registration Application Form

- ▶ currently being designed
- ▶ combined form with homeopathics
- ▶ will cover initial registration, variations, renewals
- ▶ will be on MHRA web-site when finalised
- ▶ along with a guidance note on 'How to complete the Registration Form'
- ▶ www.mhra.gov.uk

Traditional Herbal Medicinal Products

Providing Evidence of Traditional Use

Linda Anderson

Overview

- ▶ Providing Evidence of Traditional Use
- ▶ Permitted Indications for THMPD Products
- ▶ Summary of Product Characteristics (SPC)

Providing Evidence of Traditional Use

- ▶ Applicants are required to submit bibliographic or expert evidence to the effect that the medicinal product or a corresponding medicinal product has been in medicinal use throughout a period of 30 years preceding the date of application
- ▶ At least 15 of the 30 years use must relate to the EU
- ▶ Areas classified as ‘outermost regions’ are considered part of the EU
- ▶ Includes: Guyane, Guadeloupe, Martinique and Reunion (French Overseas Departments); Azores, Madeira; Canary Islands

Providing Evidence of Traditional Use

Article 16c contd:

- ▶ If product has <15 years use in EU but otherwise meets requirements can refer to Herbal Medicinal Products Committee (EMEA)

Providing Evidence of Traditional Use

- ▶ Traditional use evidence not required if on 'List' drawn up by the HMPC
- ▶ a corresponding product is one having
 - ▶▶ same herbal active ingredients but not necessarily the same excipients
 - ▶▶ same or similar intended purpose
 - ▶▶ equivalent strength and posology
 - ▶▶ same route of administration
 - ▶▶ number or quantity of ingredients may be reduced

Providing Evidence of Traditional Use

- ▶▶ will need to consider if the proposed product has the same herbal active ingredients
- ▶▶ extraction solvents
- ▶▶ drug:extract ratio

Providing Evidence of Traditional Use

Examples of sources of evidence

- ▶ **currently licensed UK herbal products**
- ▶ > 500 products in UK
- ▶ majority of UK products based on 'traditional use'
- ▶ majority on UK market for > 30 years
- ▶ for information on UK products - contact Information Centre

Providing Evidence of Traditional Use

Examples of sources of evidence

- ▶ **currently licensed EU herbal products**
- ▶ large number of products have been available in other EU countries
- ▶ > 30 years

- ▶ **official/ magistral formulations**

Providing Evidence of Traditional Use

Examples of sources of evidence

- ▶ **published information referring to specific product information**
 - ▶▶ old editions: Martindale
 - ▶▶ German Rote List
 - ▶▶ Potter's New Cyclopaedia
- ▶ **company archive materials**
 - ▶▶ brochures, sales lists, invoices

Providing Evidence of Traditional Use

Examples of sources of evidence

- ▶ other bibliographic evidence eg. text books, pharmacopoeia
- ▶ lists of traditionally used herbs from other MS eg. German, French
- ▶ documentation on use of herbal medicines manufactured as 'specials'
- ▶ evidence from herbal practitioners

Permitted Indications for THMPD Products

Article 16a

- ▶ for HMP that have indications exclusively appropriate to THMP which by virtue of their composition and purpose, are intended for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment
- ▶ must be suitable for self-medication and not need to be subject to medical prescription

Permitted Indications for THMPD Products

Article 71

- ▶ medicinal products shall be subject to prescription
- ▶ present a danger even when used correctly, if used without medical supervision
- ▶ are frequently used incorrectly and are likely to present a danger to public health
- ▶ contain substances or preparations thereof, which require further investigation
- ▶ are used parenterally

Suitability of Registered Herbal Medicines For General Sale

- ▶ GSL appropriate for medicines which can, with reasonable safety, be sold or supplied without supervision by a pharmacist
- ▶ where hazard to health and risk of misuse is small
- ▶ where no significant special precautions for handling
- ▶ where case for wider sale outweighs the benefit of professional advice at the point of sale

Suitability of Registered Herbal Medicines For General Sale

- ▶ For all OTC medicines need to ensure correct self-diagnosis/ self-treatment together with any essential safeguards required to prevent incorrect usage
- ▶ need to consider
 - ▶▶ additional information, warning statements,
 - ▶▶ restrictions on indications/use,
 - ▶▶ contra-indications,
 - ▶▶ dose, pack-size, length of treatment
 - ▶▶ circumstances requiring intervention by a doctor
 - ▶▶ action needed if symptoms do not respond or adverse reactions occur

Examples of Indications Not Likely To Be Permitted for THMPD Products

- ▶ Bone diseases
- ▶ Cardiovascular diseases
- ▶ Chronic insomnia
- ▶ Diabetes and other metabolic diseases
- ▶ Diseases of the liver, biliary system and pancreas
- ▶ Endocrine diseases
- ▶ Genetic disorders
- ▶ Joint, rheumatic and collagen diseases
- ▶ Malignant diseases

Examples of Indications Not Likely To Be Permitted for THMPD Products

- ▶ Psychiatric diseases
- ▶ Serious disorders of the eye and ear
- ▶ Serious gastrointestinal diseases
- ▶ Serious infectious diseases including HIV-related diseases and tuberculosis
- ▶ Serious neurological and muscular diseases
- ▶ Serious renal diseases
- ▶ Serious respiratory diseases
- ▶ Serious skin disorders
- ▶ Sexually transmitted diseases

Unsuitable THMPD Indications

Pre-application Notifications

- ▶ diabetes
- ▶ epilepsy
- ▶ thyroid problems
- ▶ glaucoma
- ▶ infertility
- ▶ cirrhosis of the liver

Examples of Permitted Indications THMPD Products

The gastro-intestinal system:

'symptomatic relief of':

- ▶ indigestion, heart burn, hyperacidity, dyspepsia, halitosis (bad breath) or flatulence
- ▶ colicky pain, stomach ache or nausea, occasional or non-persistent diarrhoea or constipation
- ▶ travel sickness or related symptoms

Examples of Permitted Indications THMPD Products

Infections including viral, bacterial and fungal diseases:
'symptomatic relief of':

- ▶ minor skin infections, relief of pruritus or exanthematous rashes of childhood infection and boils, athlete's foot
- ▶ common colds, coughs, conditions commonly referred to as influenza and similar upper respiratory tract infections
- ▶ minor acute inflammatory conditions of the buccal cavity and pharynx

Examples of Permitted Indications THMPD Products

The musculo-skeletal system:

‘symptomatic relief of’:

- ▶ Muscular pain and stiffness including
 - ▶▶ backache, sciatica, lumbago, fibrositis, rheumatic pain and cramp.

The respiratory system

‘symptomatic relief of’:

- ▶ Hay fever, rhinitis or catarrh.
- ▶ Blocked-up sinuses.

Examples of Permitted Indications THMPD Products

The nervous system:

‘symptomatic relief of’:

- ▶ headache including migrainous headache
- ▶ neuralgia
- ▶ difficulties falling asleep
- ▶ agitation, anxiety, irritability, nervous tension, stresses, strains, tenseness

THMPD Indications

- ▶ MHRA guidance note
- ▶ will be added to web-site
- ▶ consideration being given to suitable indications for
 - ▶▶ Hypericum
 - ▶▶ Ginkgo
 - ▶▶ Saw palmetto
 - ▶▶ Ginseng

Summary of Product Characteristics SPC

- ▶ Section 1: Name of the medicinal product
- ▶ Section 2: Qualitative and quantitative composition
- ▶ Section 3: Pharmaceutical form
- ▶ Section 4: Clinical particulars
 - ▶▶ 4.1: therapeutic indications
 - ▶▶ 4.2: posology and method of administration
 - ▶▶ 4.3: contraindications
 - ▶▶ 4.4: special warning and precautions for use
 - ▶▶ 4.5: interaction with other medicinal products and other forms of interaction

Summary of Product Characteristics SPC Contd.

- ▶▶ 4.6: pregnancy and lactation
- ▶▶ 4.7: effects on ability to drive and use machines
- ▶▶ 4.8: undesirable effects
- ▶▶ 4.9: overdose

- ▶ Section 5: Pharmacological properties
 - ▶▶ 5.1: pharmacodynamic properties
 - ▶▶ 5.2: pharmacokinetic properties
 - ▶▶ 5.3: preclinical safety data

Summary of Product Characteristics SPC Contd

- ▶ Section 6: Pharmaceutical particulars
 - ▶▶ 6.1: list of excipients
 - ▶▶ 6.2: incompatibilities
 - ▶▶ 6.3: shelf-life
 - ▶▶ 6.4: special precautions for storage
 - ▶▶ 6.5: nature and contents of container
 - ▶▶ 6.6: instructions for use and handling and disposal

Summary of Product Characteristics SPC Contd

- ▶ Section 7: Registration Holder
- ▶ Section 8: Registration number(s)
- ▶ Section 9: Date of first registration/ renewal of registration
- ▶ Section 10: Date of revision of the text

Traditional Herbal Medicinal Products

Labelling and Patient Information

Jan MacDonald

Overview

- ▶ Legislation in the UK
- ▶ Implementation of requirements in the UK
- ▶ Interpretation of the Directive
- ▶ EC guidance available
- ▶ New developments

Directive 2001/83/EC

“the provisions governing the information supplied to users should provide a high degree of consumer protection, in order that medicinal products may be **used correctly** on the basis of **full and comprehensible information**”

Directive 2001/83/EC

Package Leaflet means a leaflet containing information for the user which accompanies the medicinal product.

Article 1.26

Inclusion of a leaflet is **obligatory** unless all the information can be directly conveyed on the outer or immediate packaging

Article 58

Directive 2001/83/EC

The package leaflet shall be drawn up **in accordance with** the Summary of Product Characteristics (SmPC).

Article 59.1

Labelling Requirements

1. Product name, immediately followed by
2. Common name (if appropriate)
3. Statement of active content
4. Pack contents (weight, volume, doses)
5. Excipients of known effect

Labelling Requirements

6. Method and route of administration.
7. Store out of the reach and sight of children
8. Special warnings
9. Expiry date (Jul 03, 07/2003)
10. Storage precautions

Labelling Requirements

11. Disposal instructions
12. MA holders name
13. MA holders address
14. Product licence number
15. Batch number

Labelling Requirements

16. If intended for self-medication, **full** instructions for use

Also

- ▶▶ Legal Status
- ▶▶ Council Directive 2004/24/EC Article 16(g)(2)

Labelling Requirements

Article 16(g)(2) 2004/24/EC label and PIL must state:

- ▶ “Product x is a traditional herbal medicinal product for use in specified indication(s) exclusively based on longstanding use

and

- ▶ User should consult a doctor or a qualified healthcare practitioner if the symptoms persist during the use of the product or if adverse effects not mentioned in the package leaflet occur”

External Use

“For external use” applies to

- ▶ embrocation
- ▶ liniment
- ▶ lotion
- ▶ liquid antiseptic
- ▶ other liquid or gel preparation intended for external application

External Use

“External application” refers to

- ▶▶ skin
- ▶▶ hair
- ▶▶ teeth
- ▶▶ mucosa of mouth, throat, nose, ear, eye, vagina or anal canal

where local action only is intended and systemic absorption is unlikely to occur

Topical Application

Topical application is a route of administration for products applied to

- ▶ skin
- ▶ mucous membranes
- ▶ up the nose

Topical Application

Topical administration includes products such as

- ▶ creams and ointments applied to skin and locally absorbed
- ▶ patches applied to the skin where active ingredients is systemically absorbed in significant quantity.

Reduced Labelling

Blister foils (Directive 2001/83/EC, Article 55.2)

- ▶ Name (including strength and form)
- ▶ Common name
- ▶ Batch number and expiry date
- ▶ Name of PL holder

Reduced Labelling

Small containers (nominal volume < 10ml)
(Directive 2001/83/EC, Article 55.3)

- ▶ Name (including strength and form)
- ▶ Common name
- ▶ Method and route of administration
- ▶ Batch number and expiry date
- ▶ Contents by weight, volume or unit

Leaflet Requirements

Product Identification

- ▶ product name (1)
- ▶ common name (2)
- ▶ active content (2)
- ▶ pharmaceutical form(3)

Leaflet Requirements

Product identification

- ▶ pack size (6.5)
- ▶ excipients (6.1)
- ▶ pharmaco-therapeutic group (5.1)
- ▶ MA holder details (7)
- ▶ manufacturers details

Leaflet Requirements

- ▶ What is the medicine for ? (4.1)
- ▶ Information necessary before taking product
 - ▶▶ when not to take (4.3)
 - ▶▶ when special care is needed (4.4)
 - ▶▶ interactions (4.5)

Leaflet Requirements

- ▶ Information necessary before taking product
 - ▶▶ information for pregnant and breastfeeding patients (4.6)
 - ▶▶ effects on driving / operating machinery (4.7)
 - ▶▶ excipients of known effect

Leaflet Requirements

- ▶ Instructions for use (4.2)
 - ▶▶ usual dose for all indications and patients
 - ▶▶ how it is given
 - ▶▶ frequency of dosing and duration of treatment
 - ▶▶ overdose
 - ▶▶ missed dose
 - ▶▶ withdrawal (if relevant)

Leaflet Requirements

- ▶ Side effects (4.8)
 - ▶▶ all side effects in SmPC to be listed
 - ▶▶ action to be taken
 - ▶▶ order appropriately

Leaflet Requirements

- ▶ How to keep the medicine
 - ▶▶ storage precautions (6.4)
 - ▶▶ reconstituted / open shelf life (6.3)
 - ▶▶ safe disposal (6.4 & 6.6)
- ▶ Revision date of leaflet text

Leaflet Summary

- ▶ Patient Information Leaflets are
 - ▶▶ mandatory
 - ▶▶ in a specified order
 - ▶▶ consistent with the SmPC
 - ▶▶ written in lay language
 - ▶▶ non-promotional

EC Guidelines

- ▶ Provision made in Article 65 of Directive 2001/83/EC
- ▶ Excipients
- ▶ Readability

Excipient Guideline

- ▶ Details excipients to be declared on labelling
- ▶ Information to be included in PIL for those excipients declared on labelling

Excipient Guideline - Label

- ▶ All excipients must be declared on the labelling of injectable, topical, eye preparation and inhaled medicines.
- ▶ Excipients of known effect must be declared on the labelling of all other medicines

Excipient Guideline - Leaflet

- ▶ All excipients must be declared in leaflet including
 - ▶▶ constituents of capsule shell, film coat, polish, printing inks
 - ▶▶ pH adjusters
 - ▶▶ diluents
 - ▶▶ constituents in mixture of chemically related components (e.g preservatives)
- ▶ Translated into 'patient-friendly' terms

Readability Guideline

- ▶ Primary objective is to give guidance on the readability of the label and package leaflet.

Readability Guideline

- ▶ Model Leaflet
 - ▶▶ What the product is
 - ▶▶ Before taking
 - ▶▶ How to take
 - ▶▶ Side Effects
 - ▶▶ Storage
- ▶ User Testing

Presentation of Leaflet Information

- ▶ Take into account reading ability
- ▶ Use short sentences
- ▶ Avoid technical terms or translate
- ▶ Take care with translation
- ▶ Explain significance of instructions
- ▶ Give thought to layout
- ▶ Use colour and graphics to highlight

Principles of Best Practice Guidance

- ▶ Labelling must comply with Article 54 of Directive 2001/83/EC
- ▶ Five critical items of information identified
 - ▶▶ Name (as in section 1 of SmPC)
 - ▶▶ Strength (per unit volume & per container)
 - ▶▶ Route of administration (positive only)
 - ▶▶ Dosage (for self- medicated products)
 - ▶▶ Special warnings

Critical Information

- ▶ Where possible critical items of information should be located together on the pack (same field of view).
- ▶ Large font, line spacing to maximise legibility
- ▶ Name on at least three non-opposing faces to aid accurate identification
- ▶ Common name to be given due prominence

Effective Pack Design

- ▶ large font
- ▶ line spacing
- ▶ innovative pack design
- ▶ judicious use of colour
- ▶ space for dispensing label
- ▶ user testing

Summary

- ▶ Directive 2001/83/EC
 - ▶▶ outlines legal obligations
 - ▶▶ sets framework

- ▶ Guidelines
 - ▶▶ build on regulatory requirements
 - ▶▶ produce consistency
 - ▶▶ assist with quality

The Final Message

To provide patients with full, easily understood information leading to compliance and safe use of medicines.

Traditional Herbal Medicinal Products

Providing a Bibliographic Review of Safety

Linda Anderson

Providing A Bibliographic Review of Safety

Article 16c (d)

- ▶ The Applicant shall submit a bibliographic review of safety data together with an expert report

Article 16f

- ▶ if the herbal substance (preparation/combination) is on the list, the data do not need to be provided

HMPC

- ▶ not clear how quickly the list will be established
- ▶ UK has requested that HMPC provide guidance on bibliographic review

Providing A Bibliographic Review of Safety

- ▶ No official guidance yet
- ▶ Presentation and Format not defined
- ▶ UK proposes safety review included in Module 4
- ▶ Not clear if there will be a separate Clinical Expert Report/ Summary
- ▶ HMPC/ Commission may give guidance on format and content but when?
- ▶ Get started anyway
- ▶ Need to identify any safety concerns early on

Providing A Bibliographic Review of Safety

- ▶ Getting started - basic principles
 - ▶▶ is the herbal ingredient widely used ?
 - ▶▶ is it 'generally considered as safe'?
 - ▶▶ is it generally considered as safe by the regulators?
 - ▶▶ are there any emerging issues?
 - ▶▶ if there are - don't ignore them
 - ▶▶ especially drug: herb interactions

Providing A Bibliographic Review of Safety

- ▶ what is known about the phytochemical constituents?
- ▶ are there any 'potentially toxic / undesirable' constituents?
 - ▶▶ pyrrolizidine alkaloids
 - ▶▶ diterpenes
 - ▶▶ furanocoumarins
 - ▶▶ sesquiterpene lactones
 - ▶▶ estrogenic constituents

Providing A Bibliographic Review of Safety

- ▶ Applicants should ensure herbal ingredients
 - ▶▶ not on POM Order (Prescription Only)
 - ▶▶ not on UK Banning Orders
 - ▶▶ not on Part I SI 2130 The Medicines (Retail Sale and Supply of Herbal Remedies) Order 1977
 - ▶▶ if on Parts II and III - check with MHRA
 - ▶▶ not on CPMP List: Herbal drugs with serious risks. 1992
- ▶ If in any doubt check with MHRA

Providing A Bibliographic Review of Safety

- ▶ Presentation and Format - to be defined
- ▶ Compile bibliographic review as a list of publications with titles, authors, dates
- ▶ Possible options
 - ▶▶ Submit list as Module 4 with references available on request to MHRA
 - ▶▶ or submit full bibliography with the dossier
 - ▶▶ may depend on the ingredients/product

Providing A Bibliographic Review of Safety

- ▶ bibliographic review should cover all aspects of safety and should refer to a review of the relevant literature, taking into account any published scientific literature concerning experience in the form of epidemiological studies
- ▶ all documentation, both favourable and unfavourable should be presented
- ▶ review should consider all of the herbal ingredients and the proposed product
- ▶ information on similar products would be helpful

Providing A Bibliographic Review of Safety

If vitamins and/or minerals are included

- ▶ will need to include them in safety review
- ▶ consider significance to specific patient groups
 - ▶▶ children
 - ▶▶ pregnancy, lactation
- ▶ use with concomitant medication/ other herbal products

Sources of Information

- ▶ information on existing licensed products
 - ▶▶ UK, other Member States, rest of world
- ▶ information on use in food products/ supplements
- ▶ check General Sales List (www.mhra.gov.uk)
- ▶ EMEA web-site:
 - ▶▶ Position papers on *Aristolochia*, asarone, estragole

Sources of Information

General references

- ▶ ESCOP monographs
- ▶ WHO monographs
- ▶ British Herbal Pharmacopoeia
- ▶ British Herbal Compendium
- ▶ American Herbal Pharmacopoeia
- ▶ German Commission E Monographs
- ▶ Potter's Herbal Cyclopaedia
- ▶ Martindale
- ▶ Other authoritative publications

Sources of Information

General references contd.

- ▶ Herbal Drugs and Phytopharmaceuticals (M Wichtl ed)
- ▶ Adverse effects of herbal drugs Vols. 1-3 (De Smet ed)
- ▶ Rational Phytotherapy (Schulz ed)
- ▶ PDR for Herbal Medicines (J Gruenwald ed.)
- ▶ Council of Europe: *Flavouring Substances and natural Sources of Flavourings*
- ▶ American Herbal Products Association's *Botanical Safety Handbook*
- ▶ Specific articles on individual herbal ingredients

Sources of Information

Commercial Information databases:

- ▶ PubMed/Medline
- ▶ EMBASE (Excerpta Medica)
- ▶ BIOSIS
- ▶ Toxline
- ▶ Dialog DataStar - access to multiple databases
- ▶ Cochrane Library - systematic reviews/ meta-analyses
- ▶ Natural Medicines Comprehensive Database

What To Search For

- ▶ Non-clinical Toxicology
 - ▶▶ single dose, repeat dose toxicity
 - ▶▶ genotoxicity
 - ▶▶ carcinogenicity
 - ▶▶ reproductive and developmental toxicity
 - ▶▶ local tolerance
 - ▶▶ any other toxicity studies
- ▶ Report what is available
- ▶ What searches were carried out

What To Search For

Clinical safety

- ▶ Published clinical trials
 - ▶▶ numbers treated, posology, special patient groups
 - ▶▶ adverse events - frequency, nature and severity
- ▶ Consider patient groups at increased risk
 - ▶▶ children, elderly
 - ▶▶ pregnant women, breastfeeding
 - ▶▶ people with abnormalities of metabolism/excretion
- ▶ Potential interactions - concomitant medication/ food

Potential Drug/ Herb Interactions

- ▶ Growing recognition of potential problems due to drug/ herb interactions
 - ▶▶ Hypericum
 - ▶▶ Warfarin -
 - » Cranberry
 - » Garlic
 - » Ginseng
 - » Ginkgo

Expert Report on Safety

- ▶ Who can act as the Expert
 - ▶▶ suitable qualifications and experience
- ▶ Purpose of the Expert Report
 - ▶▶ critical analysis of the available safety data
 - ▶▶ to support product information
- ▶ Format of the Expert Report
 - ▶▶ to be confirmed

Content of The Expert Report

- ▶ discussion of the phytochemical composition of the herbal ingredients identifying any potentially hazardous constituents
- ▶ discussion of safety in relation to product quality
 - ▶▶ residues (solvents, pesticides, fumigants)
 - ▶▶ potential impurities/ degradation products
 - ▶▶ microbial limits, heavy metals
- ▶ safety aspects of added vitamins/minerals

Content of The Expert Report

- ▶ review of reported non-clinical toxicological studies
 - ▶▶ highlight findings that could affect the evaluation of safety in clinical use
- ▶ review of reported clinical studies
 - ▶▶ nature of patient population, extent of exposure
 - ▶▶ reported adverse events
 - ▶▶ relationship to dose, dose regimen, treatment duration
 - ▶▶ how to prevent, mitigate or manage adverse events
 - ▶▶ long term safety

Content of The Expert Report

Use headings of Summary of Product Characteristics

- ▶ Use in specific patients groups
- ▶ Posology
- ▶ Contraindications
- ▶ Special warning and precautions for use
- ▶ Interaction with other medicinal products and other forms of interaction
- ▶ Pregnancy and lactation
- ▶ Effects on ability to drive and use machines
- ▶ Undesirable effects
- ▶ Overdose

Content of The Expert Report

- ▶ suitability of product for use without medical intervention
- ▶ suitability of proposed product literature to ensure safe use
- ▶ overall evaluation of 'acceptable level of safety'
- ▶ overall appraisal of risk in relation to use

Traditional Herbal Medicinal Products

Quality requirements Session I

Quality Requirements

Session I

- ▶ General Principles and Requirements
- ▶ Guidelines
- ▶ European Pharmacopoeia
- ▶ Requirements for Excipients
- ▶ TSE requirements for medicinal products
- ▶ EP Certification Procedure
- ▶ Requirements for herbal active ingredients

General Principles and Requirements

- ▶ THMPD provides no derogation with regard to the necessary physico-chemical, biological, microbiological tests
- ▶ quality will be considered in relation to safety rather than efficacy - it is not appropriate to consider *quality for the sake of quality*
- ▶ but - requirements set out in Annex I to 2001/83/EC as amended apply
- ▶ applicants required to take account of CPMP and other guidelines
- ▶ European Pharmacopoeia standards are legally binding

Notes for Guidance

- ▶ Annex I:
 - ▶▶ in assembling the dossier for applications applicants shall take into account the scientific guidelines adopted by CPMP/Commission
- ▶ Applicants need to be aware of all guidelines both general and specific
- ▶ Keep up to date with any revisions to guidance documents
- ▶ www.emea.eu.int or www.mhra.gov.uk

Specific Guidance on Herbal Medicinal Products

CPMP Notes for guidance

- ▶ Quality of herbal medicinal products
CPMP/QWP/2819/00
- ▶ Specifications: test procedures and acceptance criteria for herbal drugs etc. *CPMP/QWP/2820/00*

HMPWP Points to Consider

- ▶ Points to Consider on Good Agricultural and Collection Practice for starting materials of herbal origin
EMA/HMPWP/31/99 Rev.3
- ▶ Will be updated to include CTD
- ▶ HMPC may revise guidelines to take account of THMPD

Key Notes for Guidance

- ▶ Stability testing of existing active substances and related finished products *CPMP/QWP/122/02,rev 1*
- ▶ Impurities: Residual solvents *CPMP/ICH/283/95*
- ▶ Quality of water for pharmaceutical use *CPMP/QWP/158/01 rev*
- ▶ Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products

Quality Requirements

Annex I to Directive 2001/83 (Directive 2003/63/EC)

- ▶ Article 16c says *Annex I shall apply by analogy to the particulars and documents specified at point (a)*
- ▶ Point (a) includes the pharmaceutical tests
- ▶ Annex states that:
 - ▶▶ with respect to the quality part of the dossier, all monographs including general monographs and general chapters of the European Pharmacopoeia are applicable

European Pharmacopoeia General Monographs

- ▶ requirements apply to all products in the given class
- ▶ in some cases even where there is no specific monograph
 - ▶▶ Dosage form monographs
 - ▶▶ Extracts
 - ▶▶ Tinctures
 - ▶▶ Herbal drugs,
 - ▶▶ Herbal drug preparations,
 - ▶▶ Herbal teas
 - ▶▶ Vegetable fatty oils

European Pharmacopoeia General Chapters

- ▶ Substances for pharmaceutical use
- ▶ Residual solvents (ICH guidelines)
- ▶ Products with risk of transmitting agents of animal spongiform encephalopathies
- ▶ Microbiological quality of pharmaceutical preparations

European Pharmacopoeia Methods Of Analysis

- ▶ Apparatus
- ▶ Physical and physicochemical methods
- ▶ Identification
- ▶ Limit tests
- ▶ Assays
- ▶ Methods in Pharmacognosy
- ▶ Pharmaceutical technical procedures

European Pharmacopoeia Methods in Pharmacognosy

Including:

- ▶ Ash insoluble in hydrochloric acid
- ▶ Foreign matter
- ▶ Pesticides residues (tests and limits)
- ▶ Determination of essential oils
- ▶ Determination of tannins in herbal drugs
- ▶ Bitterness value
- ▶ Dry residue of extracts
- ▶ Loss on drying of extracts
- ▶ Determination of aflatoxins - in preparation

European Pharmacopoeia Pharmaceutical Technical Procedures

Including:

- ▶ Disintegration of tablets and capsules
- ▶ Uniformity of mass
- ▶ Uniformity of content
- ▶ Friability of uncoated tablets
- ▶ Test for methanol and 2-propanol
 - ▶▶ important for ethanolic extracts

European Pharmacopoeia Materials for Containers

Including:

- ▶ materials based on non-plasticised PVC for containers for dry dosage forms for oral use
- ▶ glass containers for pharmaceutical use
- ▶ plastic containers and closures for pharmaceutical use

European Pharmacopoeia Specific Monographs

- ▶ specific monographs on herbal drugs >120
 - ▶▶ substantial work programme on herbal drugs
 - ▶▶ *Pharmeuropa - October 2004*
 - ▶▶ *draft monographs - Artichoke leaf, Centaury, Fumitory, Purple Coneflower herb and root, Rhubarb*
- ▶ specific monographs on excipients

European Pharmacopoeia

- ▶ In case where active substances or excipients are described neither in the EP nor pharmacopoeia of a Member State compliance with a third country pharmacopoeia can be accepted
- ▶ Applicant must submit a copy of the monograph plus analytical validation

Requirements for Excipients

- ▶ General requirements for excipients
 - ▶▶ Note for guidance on excipients, antioxidants and antimicrobial preservatives CPMP/QWP/419/03
 - ▶▶ under revision
- ▶ TSE requirements for medicinal products
- ▶ Certificates of Suitability

General Requirements for Excipients

Annex I

- ▶ all excipients used in manufacture must be listed identifying where each material is used in the process
- ▶ information on the quality and control has to be provided plus
- ▶ have to meet standards appropriate for their use
- ▶ colouring matter shall in all cases satisfy requirements of
 - ▶▶ Directives 78/25/EC and/or 94/36/EC
 - ▶▶ purity criteria in Directive 95/45/EC, as amended

General Requirements for Excipients

Annex I

- ▶ specific attention must be paid to excipients of human or animal origin
- ▶ novel excipients
 - ▶▶ excipients used for the first time in a medicinal product or by a new route of administration
 - ▶▶ full details of manufacture, characterisation, controls
 - ▶▶ safety data (non-clinical, clinical)
 - ▶▶ treated like ‘new active substance’

General Requirements for Excipients

Applicant must consider

- ▶ Does the EP apply?
- ▶ If so does your supplier comply with EP
- ▶ Ask for recent certificates of analysis for dossier

If excipient is not in EP

- ▶ Check if complies with national pharmacopoeia of a Member State
- ▶ If not - will need to support specification
- ▶ Note: additional requirements for 'novel excipients'
- ▶ Seek advice from MHRA if any excipients may be novel

General Requirements for Excipients

Flavouring agents

- ▶ usually natural products and/or synthetic substances
- ▶ because of their complexity - only need to describe the general qualitative composition mentioning the main constituents with an appropriate process of identification to ensure consistency of the composition (in particular, identification of the main constituents and if necessary carriers)
- ▶ provide confirmation of food use

TSE Requirements for Medicinal Products

- ▶ Minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products
- ▶ Transmissible Spongiform Encephalopathies
- ▶ CPMP/CVMP Note for Guidance Rev 2
- ▶ Animal derived materials in herbal medicinal products
- ▶ Requirements for TSE risk materials

Transmissible Spongiform Encephalopathies

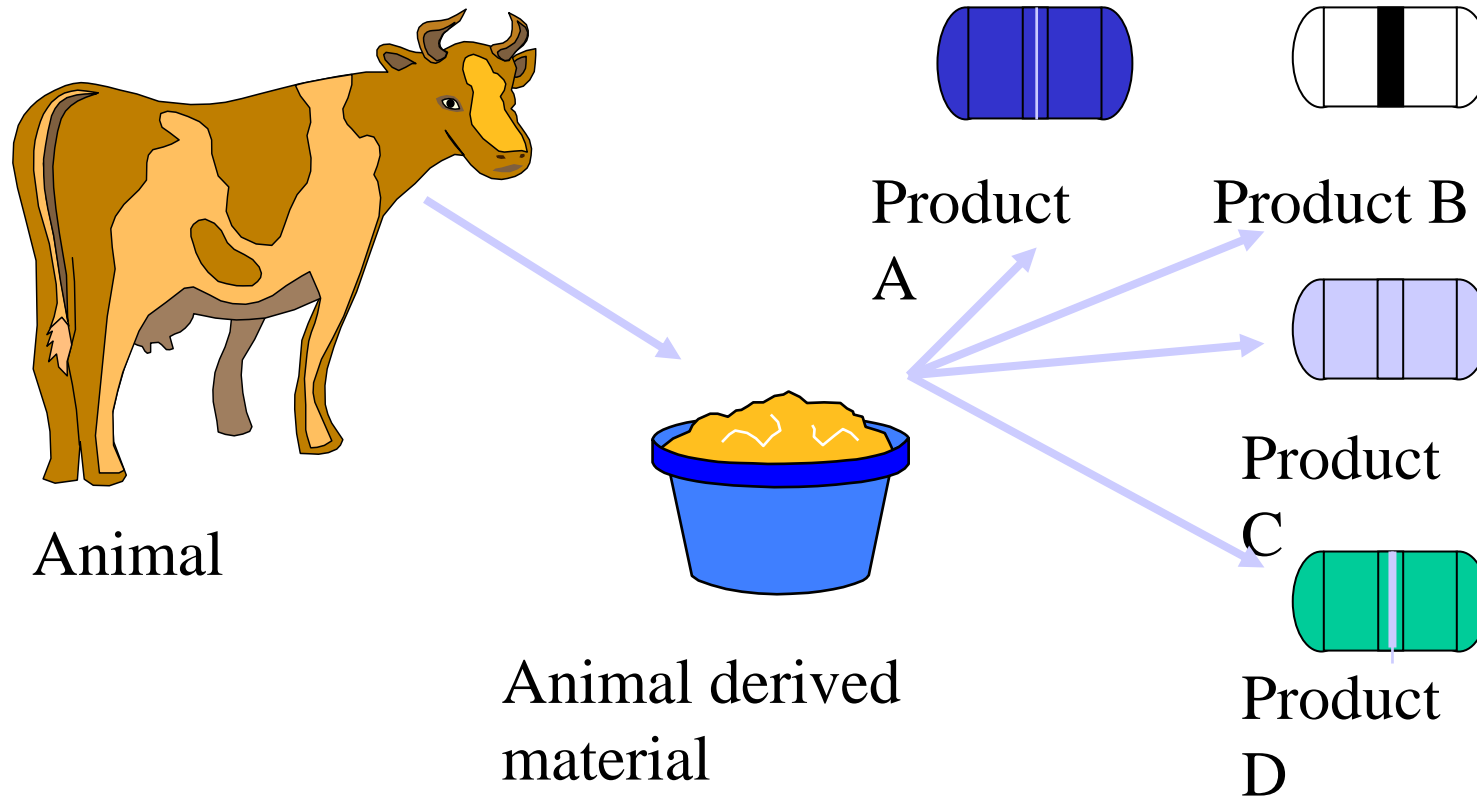
- ▶ Bovine spongiform encephalopathy (BSE) in cattle
- ▶ Scrapie in sheep and goats
- ▶ Chronic wasting disease in deer & elk
- ▶ Transmissible mink encephalopathy in farmed mink
- ▶ Creutzfeldt- Jakob disease (CJD)
- ▶ Kuru

CPMP/CVMP Note For Guidance EMA/410/01 Rev 2

- ▶ Guideline sets out key scientific principles for minimisation of risk
 - ▶▶ geographical source
 - ▶▶ selection of tissues
 - ▶▶ manufacturing procedure
- ▶ Controls in place since 1999
- ▶ Revision 2 - effective July 2004
- ▶ Further draft out for consultation - due to cases in US, Canada

Animal Derived Materials in Herbal Medicinal Products

- ▶ 80% of medicines contain animal derived materials



Animal Derived Materials in Herbal Medicinal Products

- ▶ Gelatin - Bovine bones & hide, pig hide
- ▶ Tallow Derivatives - Fat derived
 - ▶▶ e.g. glycerol, magnesium stearate, stearic acid, polysorbates
- ▶ Lactose - milk derivative
- ▶ Lanolin, wool alcohols

Animal Derived Materials in Herbal Medicinal Products

- ▶ **Gelatin** - alkaline process, GBR category I, II & II countries- acid process, GBR category I, II countries
- ▶ **Tallow derivatives** - harsh processing - animal tissue may be derived from any country
- ▶ **Milk and materials derived only from milk** are excluded from the guideline provided the milk is sourced from healthy animals.
- ▶ **Wool and hair derivatives** e.g. lanolin, wool alcohols and amino acids are excluded provided the wool and hair are sourced from live animals or slaughtered animals fit for human consumption and manufactured by a rigorous process

Requirements for TSE Risk Materials

- ▶ The applicant must demonstrate that the medicinal product is manufactured in accordance with the Note for Guidance on Minimising the Risk of transmitting TSE
- ▶ Easiest way - provide evidence that the excipient is covered by a current Certificate of suitability of the European Pharmacopoeia (CEP)
- ▶ Applicant must submit copy of CEP
- ▶ In the absence of a certificate of suitability, dossier containing appropriate documentation must be submitted - additional fees charged
- ▶ Applicants urged to use suppliers with CEPs

European Pharmacopoeia Certification Procedure

- ▶ Official procedure since 1994
- ▶ Purpose
- ▶ To avoid duplication of work
 - ▶▶ by manufacturers of raw materials
 - ▶▶ by applicants in preparing licensing dossiers
 - ▶▶ by National and European Licensing Authorities in the assessment process
- ▶ To eliminate differences in interpretation of monographs by various Licensing Authorities

Scope of The Certification Procedure

- ▶ The procedure is intended to be used for substances for which a monograph (general monograph and/or specific monograph) has been adopted by the EP Commission
- ▶ Organic or inorganic substances (actives/excipients)
- ▶ Fermentation products
- ▶ TSE risk materials
- ▶ Recently extended to include Herbal drugs and Herbal drug preparations
- ▶ Procedure does not cover finished dosage forms

Certification Procedure

- ▶ Application submitted to European Directorate for the Quality of Medicines (EDQM) in Strasbourg
- ▶ Consists of:
 - ▶▶ Application form
 - ▶▶ Two copies of dossier
 - ▶▶ Expert Report
 - ▶▶ Samples of substances with Certificates of Analysis
 - ▶▶ Fee
- ▶ Assessed by rapporteur/co-rapporteur - mainly assessors from national authorities

Content of CEP Dossier

TSE Risk Assessment

- ▶ General Information
- ▶ Origin of raw material and type of tissue used
- ▶ Manufacturing Process
- ▶ Traceability
- ▶ Auditing System
- ▶ Expert Report

Content of CEP Dossier

Herbal Drugs and Herbal Drug Preparations Quality Evaluation

- ▶ guidance available from EDQM
- ▶ CTD format and headings
 - ▶▶ Quality Overall Summary
 - ▶▶ Module 3
- ▶ particular emphasis on possible impurities originating from the production especially - heavy metals, pesticide, fumigant residues, microbial contamination, mycotoxins

Certification Further Information

▶ <http://www.pheur.org>

Traditional Herbal Medicinal Products

Requirements for Herbal Active Ingredients

Requirements for Herbal Active Ingredients

- ▶ challenges presented by herbal medicinal products
- ▶ requirements for herbal active ingredients
- ▶ considerable interest world wide in herbal medicinal products - especially quality of raw materials
- ▶ important items of commerce and international trade
- ▶ increased status in many pharmacopoeias
- ▶ increasing literature on quality aspects eg.
 - ▶▶ American Herbal Pharmacopoeia
 - ▶▶ Monographs on Chinese plants

Quality Requirements

WHO work programme

- ▶ Quality control methods for medicinal plant materials
- ▶ Good Agricultural and Collection Practices (GACP)
- ▶ Good Manufacturing Practice
 - ▶▶ Supplementary guidelines for manufacture of herbal medicinal products - being updated
- ▶ Guidelines for assessing safety and quality of herbal medicines with reference to contaminants and residues - in preparation
- ▶ Specific monographs on individual ingredients

Challenges Presented by Herbal Medicinal Products

Herbal products present unique problems

- ▶ some medicinal plants are cultivated but many still collected from the wild
- ▶ most herbal ingredients come from the field to the factory - along with soil, dirt, insects etc
- ▶ medicinal plants grown in diverse climatic regions often with high temperature, humidity, rainfall
- ▶ pre and post-harvest treatments give rise to contaminants/ residues
- ▶ microbiological contamination is of particular concern
- ▶ potential for microbial/ fungal spoilage

Challenges Presented by Herbal Medicinal Products

- ▶ plants and their phytochemical constituents vary with environmental factors
- ▶ complex mixtures of phytochemical constituents
- ▶ herbal products - usually consist of mixtures of herbal ingredients
- ▶ especially the case with THMPD products

Challenges Presented by Herbal Medicinal Products

Major challenge

- ▶ despite vast advances in phytochemistry
- ▶ lack of knowledge on constituents responsible for therapeutic activity
- ▶ lack of understanding about potential synergy
- ▶ need to consider the herbal drug/preparation in its entirety as the active substance

Challenges Presented by Herbal Medicinal Products

Herbal medicinal products

- ▶ with known active constituents eg. anthraquinones: Senna, Cascara, Frangula
- ▶ with constituents believed to contribute to therapeutic activity eg. St John's Wort
- ▶ without constituents with known therapeutic activity eg. Valerian

Challenges Presented by Herbal Medicinal Products

- ▶ “consistent quality for products of herbal origin can only be assured if the starting materials are defined in a rigorous and detailed manner including especially the specific botanical identification of the plant material used”
- ▶ “it is also important to know the geographical source and the conditions under which the herbal drug is obtained to ensure material of consistent quality”

Variability of Plant Constituents

St John's Wort

- ▶ hypericin and pseudohypericin
- ▶ 1998-2000 (38 batches)
- ▶ yield 0.06 -0.19%

Valerian

- ▶ valerenic acids
- ▶ 1997-2000 (116 batches)
- ▶ yield 0.07 - 0.50%

Why Control Quality?

“Quality cannot be confirmed simply by testing the end product. There needs to be assurance that, at every stage in the chain from receipt of raw materials to the delivery of the finished product to the consumer, systems and controls are in place which will ensure the required quality standard is achieved.”

Guidelines on GMP for manufacturers of food supplements CRN & HFMA 1997

Why Control Quality?

“ 75% of US herbal products are of poor quality”

Dr Gail Mahady, WHO Collaborating Centre, Univ. of Illinois, Chicago, June 2002

What Can Go Wrong?

- ▶ wrong plant
 - ▶▶ eg. *Aristolochia*; *Japanese Star Anise*, *Teucrium*
- ▶ right plant but a toxic plant
 - ▶▶ eg. *Aconitum*, *Senecio*
- ▶ related species: inferior quality
- ▶ other plant parts
- ▶ poor quality plants or exhausted plant material

What Can Go Wrong?

contamination - accidental

- ▶ pesticide residues,
- ▶ fumigant residues
- ▶ microbial levels,
- ▶ aflatoxins
- ▶ foreign matter - stones, soil
 - ▶▶ patient reported 'something moving about'
 - ▶▶ *Hymenoptera parasitica* (parasitic wasps)

What Can Go Wrong?

- ▶ poor storage conditions
 - ▶▶ incomplete drying - growth of bacteria/molds
 - ▶▶ infestations: mainly insects (beetles), moths, mites
 - ▶▶ atmospheric oxidation - essential and fixed oils
- ▶ deliberate adulteration
 - ▶▶ poor quality materials, other plant parts
 - ▶▶ conventional drugs, steroids, fenfluramine etc.

Key Quality Issues for Herbal Products

To ensure

- ▶ plant species correct
- ▶ herbal drug /herbal drug preparations are of suitable quality
- ▶ all other ingredients are of suitable quality
- ▶ reproducible manufacturing process
- ▶ reproducible finished product
- ▶ acceptable stability for proposed shelf-life
- ▶ storage conditions defined

THMPD Products

- ▶ pharmaceutical requirements will depend on specific dosage form
- ▶ oral use
 - ▶▶ herbal teas, tablets, hard capsules, soft capsules
 - ▶▶ oral solutions, suspensions
- ▶ cutaneous use:
 - ▶▶ creams, ointments
- ▶ eye and ear preparations
- ▶ rectal, vaginal, inhalation

Module 3: Herbal Drug

3.2.S.1: General Information

Nomenclature

- ▶ provide the binomial scientific name of the plant, chemotype parts of plants,
- ▶ definition of the herbal substance
- ▶ other names/synonyms/ laboratory code

Structure

- ▶ description of constituents with known therapeutic activity or markers
- ▶ molecular formula, relative molecular mass, structural formula, including relative and absolute stereochemistry
- ▶ information on other known constituents

Module 3: Herbal Drug

3.2.S.2: Manufacture

- ▶ details of suppliers, proposed site or facility involved in production/collection and testing of the herbal drug
- ▶ information on the plant production and plant collection including the geographical source
- ▶ cultivation, harvesting, drying and storage conditions
- ▶ pre and post-harvest chemical treatments
 - ▶▶ eg. pesticides, fumigants
- ▶ process development
- ▶ summary of the development of the active ingredient
- ▶ discuss phytochemical composition of the active ingredient

Module 3: Herbal Drug

3.2.S.3: Characterisation

- ▶ information on the botanical, macroscopical, microscopical, phytochemical characterisation, biological activity
- ▶ information on additional features which distinguish the herbal drug from potential adulterants/substitutes
- ▶ potential impurities originating from the production
 - ▶▶ potential adulterants/substitutes/contaminants
 - ▶▶ foreign matter, inorganic impurities
 - ▶▶ pesticide, fumigant residues
 - ▶▶ water content, microbial limits, mycotoxins, degradation products

Module 3: Herbal Drug

3.2.S.4: Control Of Drug Substance

- ▶ Specification for herbal drug
- ▶ Analytical procedures and validation
- ▶ Batch analyses (at least 2 batches; include batch histories; actual figures)
- ▶ Justification of specification

Requirements For Herbal Drugs

Where the herbal drug the subject of a monograph in EP or pharmacopoeia of an EU Member State

- ▶ this is the minimum legal standard
- ▶ must comply with monograph
- ▶ can refer to pharmacopoeia of a third country (eg. USP) evidence/data to support the specification needed
- ▶ where no pharmacopoeial monograph exists must draw up comprehensive specification modelled on EP

EP Monograph Headings For Herbal Drugs

- ▶ Definition
- ▶ Characters
- ▶ Identification: macroscopic, microscopic, chromatographic (TLC)
- ▶ Tests: foreign matter, other species, loss on drying, total ash, acid insoluble ash, water soluble extractive, extractable matter
- ▶ Assay: known therapeutic constituents or quality markers

St John's Wort

	EP Monograph	USP Monograph
Hypericins	Nlt 0.08% UV assay	Nlt 0.04% HPLC assay
Hyperforin	---	Nlt 0.6% HPLC assay

Assay For Herbal Drugs

	EP Monograph	USP Monograph
Valerian	Essential oil Valerenic acids Nlt 0.17%	Essential oil Valerenic acids Nlt 0.05%
Saw palmetto	Fatty acids Nlt 11%	Fatty acids Nlt 9% Lipophilic extract nlt 7%

Draft EP Monograph Purple Coneflower Herb

- ▶ *Echinacea purpurea* (L.) Moench
- ▶ Definition: dried whole or cut flowering aerial parts, minimum 0.1% total phenols calc. as sum of caftaric and cichoric acids
- ▶ Characters: macroscopic, microscopic ID tests
- ▶ Identification:
 - ▶▶ macroscopical
 - ▶▶ microscopical
 - ▶▶ TLC : using caffeic acid, chlorogenic acid
 - ▶▶ HPLC:

Draft EP Monograph Purple Coneflower Herb

- ▶ Tests: foreign matter 2%
- ▶ Loss on drying: max. 10%
- ▶ Total ash: max. 10%

- ▶ Assay: HPLC - type chromatogram
 - ▶▶ determine caftaric and cichoric acids

Additional Tests For Herbal Drugs

Additional tests may be needed for:

- ▶ potential contaminants
 - ▶▶ pesticide/ fumigant residues
 - ▶▶ microbial levels, mycotoxins
 - ▶▶ heavy metals/ toxic elements
- ▶ undesirable constituents
- ▶ degradation products
- ▶ related species
- ▶ case by case depending on herbal drug
- ▶ need to justify absence of tests, frequency of tests

Potential Impurities

- ▶ Pesticide residues
 - ▶▶ EP Test method (GC),
 - ▶▶ limits for 34 compounds
 - ▶▶ those not listed controlled by EC 76/895, 90/642
- ▶ Fumigant residues
 - ▶▶ note: ethylene oxide banned in EU
 - ▶▶ methyl bromide, phosphine, phosgene

EP Microbial Limits

Category	3B	4A	4B
TVC	10^4	10^7	10^5
Fungi	10^2	10^5	10^4
Enterobact.	10^2		10^3
E. coli	absent/1g	10^2	absent/1g
Salmonella	absent/10g		absent/10g
Stap.aureus	absent/1g		

Requirements for Herbal Drug Preparations

Herbal drug preparations - defined in legislation

- ▶ are obtained by subjecting herbal drugs to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation
- ▶ include comminuted or powdered herbal drugs, tinctures, extracts, essential oils, expressed juices and processed exudates

Module 3: Herbal Drug Preparation

3.2.S.1: General Information

Nomenclature

- ▶ provide the binomial scientific name of the plant, chemotype parts of plants,
- ▶ definition of the herbal drug preparation
- ▶ ratio of herbal drug to herbal drug preparation
- ▶ other names/synonyms/ laboratory code

Module 3: Herbal Drug Preparation

3.2.S.1: General Information

Structure

- ▶ description of constituents with known therapeutic activity or markers
- ▶ molecular formula, relative molecular mass, structural formula, including relative and absolute stereochemistry
- ▶ information on other known constituents

Module 3: Herbal Drug Preparation

3.2.S.2: Manufacture

- ▶ details of manufacturers and proposed site or facility involved in manufacturing and testing of the herbal drug preparation
- ▶ full details of the manufacturing process and process controls for the herbal preparations
- ▶ description of processing
- ▶ solvents and reagents
- ▶ purification stages
- ▶ any standardisation steps

Module 3: Herbal Drug Preparation

3.2.S.3: Characterisation

- ▶ information on the phyto- and physicochemical characterisation and biological activity
- ▶ potential impurities from the herbal drug
 - ▶▶ pesticides/ fumigant residues
- ▶ process impurities eg. solvents, catalysts
- ▶ degradation products
- ▶ microbial levels
- ▶ control of undesirable constituents

Module 3: Herbal Drug Preparation

3.2.S.4: Control Of Drug Substance

- ▶ specification for the herbal drug preparation
- ▶ analytical procedures and validation
- ▶ batch analyses (at least 2 batches; include batch histories; actual figures)
- ▶ justification for the specification

Requirements For Herbal Drug Preparations

- ▶ Where the herbal drug preparation is the subject of a monograph in EP or pharmacopoeia of an EU Member State
- ▶ This is the minimum legal standard
- ▶ Must comply with monograph
- ▶ Can refer to pharmacopoeia of a third country (eg. USP) evidence/data to support the specification needed
- ▶ Where no pharmacopoeial monograph exists must draw up comprehensive specification modelled on EP

EP Monograph Headings For Herbal Drug Preparations

- ▶ Definition
- ▶ Production
- ▶ Characters
- ▶ Identification: chromatographic
- ▶ Tests: ethanol content,
control of methanol/ 2-propanol
- ▶ Assay: known therapeutic constituents or
quality markers

EP Herbal Drug Preparations

Extracts

- ▶ Liquid extracts, Tinctures, Soft extracts, Dry extracts

Types:

- ▶ standardised - constituents known therapeutic activity
- ▶ quantified - defined range of marker substances
- ▶ others - defined by production process

Additional Tests for Herbal Drug Preparations

- ▶ potential impurities from the herbal drug
 - ▶▶ pesticides/ fumigant residues
- ▶ process impurities eg. solvents, catalysts
- ▶ degradation products
- ▶ microbial levels
- ▶ control of undesirable constituents
- ▶ case by case depending on herbal drug preparation, starting materials, method of manufacture
- ▶ need to justify absence of tests, frequency of tests

Requirements for Herbal Drug Preparations

- ▶ Need to name specific suppliers in dossier
- ▶ Will the supplier provide information to you
- ▶ Drug Master File (DMF)
- ▶ EP Certificate of Suitability
- ▶ Consider GACP (Good Agricultural and Collection Practices) aspects
- ▶ If more than one supplier - are the extracts essentially similar? Do you have evidence of this?

Traditional Herbal Medicinal Products

Quality requirements Session II

Quality Requirements Session II

- ▶ Requirements for finished products
 - ▶▶ finished product specifications
- ▶ Stability
 - ▶▶ general requirements
 - ▶▶ specific requirements for herbal products

Module 3

Herbal Medicinal Products

- ▶ 3.2.P.1 Description and composition
- ▶ 3.2.P.2 Pharmaceutical development
 - ▶▶ components of the medicinal product
 - ▶▶ active ingredients
 - ▶▶ excipients
 - ▶▶ ancillary vitamins/minerals
 - ▶▶ formulation development
 - ▶▶ overages
 - ▶▶ physiocochemical/biological properties

Module 3

Herbal Medicinal Products

- ▶ Manufacturing process development
- ▶ Container/closure system
- ▶ Microbiological attributes
- ▶ Compatibility
- ▶ 3.2.P.3 Manufacture
- ▶ 3.2.P.4 Control of excipients
- ▶ 3.2.P.5 Control of finished product
- ▶ 3.2.P.6 Reference standards/materials
- ▶ 3.2.p.7 Container/closure system
- ▶ 3.2.P.8 Stability

Control of Finished Product

- ▶ must have a finished product specification
- ▶ Nfg: Specifications: test procedures and acceptance criteria for herbal drugs etc. *CPMP/QWP/2820/00*
 - ▶▶ sets out 'core specifications' applicable to all herbal medicinal products
 - ▶▶ addresses specific dosage forms
 - » tablets, hard capsules, oral liquids

Control of Finished Product

- ▶ appropriate pharmaceutical tests
 - ▶▶ disintegration, hardness, friability
- ▶ identification tests for
 - ▶▶ herbal ingredients
 - ▶▶ vitamins, minerals (where appropriate)
 - ▶▶ preservatives
 - ▶▶ colouring matter
 - ▶▶ usually chromatographic (TLC)
 - ▶▶ challenging with combination products

Control of Finished Product

- ▶ limits for microbial contamination
 - ▶▶ would expect compliance with EP category 3B oral preparations for extracts/ tinctures
 - ▶▶ EP category 4A/4B may be justified for products containing herbal drugs
 - ▶▶ frequency of testing to be specified
 - ▶▶ at least 1 in 10 batches / annually

Control of Finished Product Assay

Assay

- ▶ constituents with known therapeutic activity or
- ▶ where no constituents with known therapeutic activity assay marker substances or other justified determinations are required
- ▶ with combinations of active ingredients where it is not possible to perform a quantitative determination for each active ingredient- may be carried out jointly

Quality of herbal medicinal products *CPMP/QWP/2819/00*

Specifications: test procedures and acceptance criteria for herbal drugs
etc. *CPMP/QWP/2820/00*

Control of Finished Product Assay

- ▶ major challenge for many THMPD products
- ▶ possible further discussion within HMPC
 - ▶▶ herbal teas
 - ▶▶ herbal drugs in capsules
 - ▶▶ mixtures of herbal drugs in capsules
 - ▶▶ combination products in general
- ▶ may be possible to adapt test methods in EP monographs on herbal drugs/ extracts

Traditional Herbal Medicinal Products

Quality requirements Session II

Stability Requirements

- ▶ General requirements
 - ▶▶ guidelines
 - ▶▶ test conditions etc
 - ▶▶ declaration of storage conditions
- ▶ Specific requirements for herbal products

General Requirements for Stability

What guidance exists

- ▶ Notice to Applicants
- ▶ Existing Guidelines: ICH, CPMP

What are common deficiencies?

Why Do Stability Studies?

“To determine how the quality of a drug substance or product varies with time and influence of factors such as temperature, humidity and light, in order to establish appropriate storage conditions, re-test periods and shelf-life”.

Why Do Stability Studies?

Directive 2001/83EEC

- ▶ Shelf-life
- ▶ Stability tests

Directive 2003/83EEC

- ▶ Revised Annex 1 to Directive 2001/83EEC
- ▶ Description of studies to determine shelf-life, storage conditions and check specification

Why Do Stability Studies?

Directive 2003/83EEC (cont.)

- ▶ Summarise types of studies conducted, protocols used and the results of the studies
- ▶ Detailed results of stability studies, including information on the analytical procedures used to generate the data and validation of these procedures presented in appropriate format
- ▶ Post authorisation stability protocol and stability commitment provided

Regulatory Guidelines

- ▶ Purpose?
 - ▶▶ to avoid unnecessary duplication of effort
- ▶ ICH
 - ▶▶ aim: international harmonisation
 - ▶▶ mutually acceptable data package
- ▶ CPMP
 - ▶▶ aim: facilitate mutual recognition/ centralised
- ▶ Should not be a regulatory strait-jacket
- ▶ Provided - justify deviations

ICH Guidelines

- ▶ Q1A: Stability Testing of New Drug Substances and products 1993 Revised November 2000 and February 2003
- ▶ Q1B: Stability Testing: Photostability Testing of New Drug Substances and Products 1996
- ▶ Q1C: Stability Testing: Requirements for New Dosage Forms 1996.
- ▶ Q1D: Note for Guidance on Bracketing and Matrixing for Stability Testing of Drug Substances and Drug Products 2002
- ▶ Q1E: Evaluation of Stability Data 2003

ICH Guidelines (cont.)

- ▶ Q1F: Stability data Package for registration Applications in Climatic Zones III and IV. February 2003
- ▶ Q2A: Validation of Analytical Procedures: Definitions and Terminology 1994
- ▶ Q2B: Validation of Analytical Procedures: Methodology 1996

CPMP Guidelines: Stability

- ▶ Stability testing of existing active substances and related finished products
- ▶ Maximum shelf-life for sterile products for human use after first opening or following reconstitution
- ▶ Declaration of storage conditions in the product particulars
- ▶ In-use stability testing of human medicinal products

ICH: Q1A(R)

Stability Testing of New Drug Substances and Products

- ▶ applies to new chemical entities
- ▶ key guideline - sets out core requirements:
 - ▶▶ test conditions
 - ▶▶ batch size/ number
 - ▶▶ evaluation

Key CPMP Guideline for Herbal Medicinal Products

Stability testing of existing active substances and related finished products CPMP/QWP/122/02 Rev1

- ▶ covers existing active substances
- ▶ mirrors parent ICH guideline on core storage conditions
- ▶ specific mention of herbal drugs, herbal drug preparations and herbal medicinal products

Active Substances

Stress testing : Not required.

- ▶ EP substance or in a national pharmacopoeia of a Member State *and* degradation products are named
- ▶ Published data on degradation

Long term / accelerated testing : Not required.

- ▶ EP substance or in a national pharmacopoeia (MS) provided monograph covers degradation products, suitable limits etc.
- ▶ Retest period defined.
- ▶ Active substance complies with monograph immediately prior to manufacture.

Active Substances

Two Options.

- ▶ **A)** 6 months data on a minimum 2 industrial-scale batches at submission
- ▶ Additional production batch added post approval
- ▶ **B)** 12 months data on a minimum 3 pilot scale (same synthetic route and process)

- ▶ 3 Production batches to be put on trial post approval

Active Substances

GENERAL CASE

	Conditions	Time at Submission
Long Term	$25^{\circ}\text{C}\pm 2^{\circ}\text{C}/60\% \pm 5\%\text{RH}$ or $30^{\circ}\text{C}\pm 2^{\circ}\text{C}/65\% \pm 5\%\text{RH}$	6 months (Option A and B))
Intermediate	$30^{\circ}\text{C}\pm 2^{\circ}\text{C}/65\% \pm 5\%\text{RH}$	6 months
Accelerated	$40^{\circ}\text{C}\pm 2^{\circ}\text{C}/75\% \pm 5\%\text{RH}$	6 months

Active Substances

Temperature sensitive products

Long term **$5^{\circ} \pm 3^{\circ}\text{C}$** **6 months (Option A and B)**

Accelerated **$25^{\circ}\text{C} \pm 2^{\circ}\text{C} / 60\% \pm 5\%\text{RH}$** **6 months**

Storage in a Freezer

Long term **$-20^{\circ} \pm 5^{\circ}\text{C}$** **6 months (Option A and B)**

Finished Products

Two Options

- ▶ **A)** 6 months data on a minimum two pilot batches of conventional dosage forms with stable active substances
- ▶ **B)** 12 months data on 3 pilot batches for critical dosage forms or where unstable active substances
- ▶ **Note:** Pilot process should meaningfully simulate production scale yielding product of quality intended for marketing
- ▶ First 3 production batches on trial post approval.

Finished Products

GENERAL CASE

	Conditions	Time to Submission
Long Term	25°C±2°C/60% ±5%RH or 30°C±2°C/65% ±5%RH	6 months (Option A) 12 months (Option B)
Intermediate	30°C±2°C/65% ±5%RH	6 months
Accelerated	40°C±2°C/75% ±5%RH	6 months

Aqueous Based Products in Semi-permeable Containers

Conditions

Time to Submission

Long Term 25°C±2°C/40% ±5%RH

or 30°C±2°C/35% ±5%RH

6 months (Option A)

12 months (Option B)

Intermediate 30°C±2°C/65% ±5%RH

6 months

Accelerated 40°C±2°C/nmt 25%RH

6 months

General Requirements For Temperature Sensitive Products

Storage in Refrigerator

Long term	$5^{\circ} \pm 3^{\circ}\text{C}$	6 months (Option A) 12 months (Option B)
Accelerated	$25^{\circ}\text{C} \pm 2^{\circ}\text{C} / 60\% \pm 5\%\text{RH}$	6 months

Storage in a Freezer

Long term	$-20^{\circ} \pm 5^{\circ}\text{C}$	6 months (Option A) 12 months (Option B)
------------------	---	--

Annex I of Guideline

An active substance is considered as stable if it is within the defined/regulatory specifications when stored for at least 2 years at 25°C/60% RH or at the alternative storage condition 30°C/65% RH and for at least 6 months at 40°C/75% RH.

Annex II of Guideline

Extrapolation of data

- ▶ If real time data is supported by accelerated studies may extrapolate beyond real time studies
- ▶ Normally extrapolation to twice length of real time data
- ▶ Maximum shelf-life of 3 years if based on extrapolation

Common Deficiencies in Stability Studies

- ▶ Test conditions
 - ▶▶ outside guidelines, undefined, no accelerated
- ▶ Batches
 - ▶▶ too small, too few, out of spec at time zero, not market pack
- ▶ Test methods and results
 - ▶▶ not stability-indicating,
 - ▶▶ data insufficient to support shelf-life/storage conditions

Most Common Deficiencies in Stability Studies

- ▶ Failure to take note of the minimum stability data required at submission
- ▶ Failure to read Annex II of the Nfg on *Stability testing of existing active substances and related finished products*
- ▶ Annex II: Extrapolation of data
 - ▶▶ If real time data is supported by accelerated studies - you may extrapolate beyond real time studies
 - ▶▶ Normally to twice length of real time data
 - ▶▶ Max 3 years if based on extrapolation

Declaration of Storage Conditions in The Product Particulars

- ▶ Nfg: Declaration of storage conditions in the product particulars
- ▶ **Core storage statements:**
 - ‘Do not store above 30 °C’ or ‘store below 30 °C’
 - ‘Do not store above 25 °C’ or ‘store below 25 °C’
 - ‘Store at 2 °C-8 °C’
 - ‘Store in a refrigerator or store and transport refrigerated
 - ‘Store in a freezer’ or store and transport frozen

Declaration of Storage Conditions in The Product Particulars (Cont)

- ▶ **Additional Labelling Statements**

 - ‘Do not refrigerate or freeze’

 - ‘Do not freeze’

- ▶ **General Storage Statements:**

 - ‘Keep container tightly closed’

 - ‘Store in the original package/container’

 - ‘Keep container in the outer carton’

Specific requirements for herbal medicinal products

Specific Requirements for Herbal Medicinal Products

- ▶ Specific guidance on herbal medicinal products
- ▶ What stability tests are required
- ▶ What to test for

Specific Requirements for Herbal Medicinal Products

- ▶ Essential to demonstrate stability to support proposed shelf-life and storage conditions
- ▶ Guidelines lay down core conditions etc
- ▶ Note for guidance on Existing active substances and related finished products - will apply
- ▶ Offers some concessions for herbal applications

Specific Stability Requirements for Herbal Medicinal Products

- ▶ need 6 months data when submitted on at least 2 pilot scale batches
- ▶ possible extrapolation to twice long term data
- ▶ if you plan to submit October 2005
 - ▶▶ need to start stability studies by March 2005 to ensure application valid (6 months data)
- ▶ if you want a longer shelf-life - you need to start before that
 - can extend by variation
- ▶ but don't start stability studies until formulation/ packaging are finalised!

What Guidance Applies

- ▶ Note for guidance on Existing active substances and related finished products
- ▶ Quality of Herbal Medicinal Products (CPMP/QWP/2819/00)
- ▶ Specifications: test procedures and acceptance criteria for herbal drugs, herbal drug preparations and herbal medicinal products (CPMP/QWP/2820/00)

Note for Guidance on Existing Active Substances and Related Finished Products

- ▶ “for active substances in EP or national pharmacopoeia data on stability tests on active substances may not be required provided that they comply with monographs immediately before manufacture of finished product”
- ▶ only applies where substance is EP or other EU national pharmacopoeia with degradation products defined
- ▶ “where herbal drugs are used as starting materials for herbal drug preparations (extracts etc) shall comply with specification before use”

Note for Guidance on Existing Active Substances and Related Finished Products

- ▶ Stability data may not be required if herbal drug or preparation complies with specification immediately prior to use
- ▶ However, establishing a retest period will enable manufacturer to hold stocks of raw materials
- ▶ Stress testing
 - ▶▶ Nfg: “usually considered unnecessary for herbal drugs and preparations”

Note for Guidance on Existing Active Substances and Related Finished Products

- ▶ To establish retest period for herbal drugs/ preparations
- ▶ Two Options
 - ▶▶ **A)** 6 months data on a minimum 2 industrial-scale batches at submission at 25°C/60% RH
 - ▶▶ **B)** 12 months data on a minimum 3 pilot scale at 25°C/60% RH

Note for Guidance on Existing Active Substances and Related Finished Products

- ▶ testing at accelerated/intermediate conditions may be omitted for herbal drugs etc if justified
- ▶ can reduce testing frequency for herbal drugs etc if justified
- ▶ container/closure same or simulating market pack

Note for Guidance on Existing Active Substances and Related Finished Products

- ▶ Establishing shelf-life/storage conditions for finished product

Two Options

- ▶ **A)** 6 months data on a minimum two pilot batches of conventional dosage forms with stable active substances
- ▶ **B)** 12 months data on 3 pilot batches for critical dosage forms or where unstable active substances
- ▶ Container/closure must be as intended for market

Note for Guidance on Existing Active Substances and Related Finished Products

GENERAL CASE

	Conditions	Time to Submission
Long Term	25°C±2°C/60% ±5%RH or 30°C±2°C/65% ±5%RH	6 months (Option A) 12 months (Option B)
Intermediate	30°C±2°C/65% ±5%RH	6 months
Accelerated	40°C±2°C/75% ±5%RH	6 months

Note for Guidance on Existing Active Substances and Related Finished Products

- ▶ No concession for herbal products with regard to accelerated storage conditions
- ▶ Can reduce testing frequency for herbal drugs etc if justified

Stability of Herbal Medicinal Products

- ▶ What to test for?
- ▶ Have to consider the unique features of herbal medicinal products
- ▶ Have to consider stability of :
 - ▶▶ starting herbal drug
 - ▶▶ herbal drug preparation
 - ▶▶ finished HMP

Stability of Herbal Medicinal Products

Unique features of HMP

“Ensuring the potency of HMP is much more complicated than ensuring the potency of chemical drugs because herbal drugs contain hundreds of compounds, often ranging between the extremes of water-solubility to fat-solubility and between different degrees of activity.”

Dr F.Gaedcke, Pharmeuropa, February 2001

Unique Features of HMP

- ▶ For most herbal drugs the chemical constituents responsible for the claimed therapeutic activity are unknown or not fully defined
- ▶ Entire herbal preparation is therefore considered as the “active substance”

Stability of Herbal Medicinal Products

Where active constituents are known

- ▶ need assay for content (Nfg on Quality of HMP)
- ▶ they often exist as a group of related substances and not as a single entity eg. Sennosides in Senna
- ▶ ? need to set limits for individual constituents

Stability of Herbal Medicinal Products

Where active constituents are unknown

- ▶ assays of marker substances (Nfg Quality of HMP)
- ▶ marker substances are chemically defined constituents of a herbal drug used for quality control purposes whether they have any therapeutic activity or not
- ▶ markers are used to calculate the quantity of herbal drug/preparation in the HMP

Stability of Herbal Medicinal Products

- ▶ HMP with constituents believed to contribute to therapeutic activity- often more than one class of constituents with pharmacological activity
- ▶ St John's Wort (*Hypericum*)
 - ▶▶ naphodianthrones (hypericin)
 - ▶▶ prenylated terpenoids (hyperforin),
 - ▶▶ flavonoids, tannins

Stability of Herbal Medicinal Products

- ▶ THMPD products frequently consist of a mixture of herbal ingredients
- ▶ many products have >5 plants as “active ingredients”
- ▶ some classes of active constituents well known to be unstable eg. volatile oils, fixed oils
- ▶ degradation products poorly characterised for most herbal drug preparations

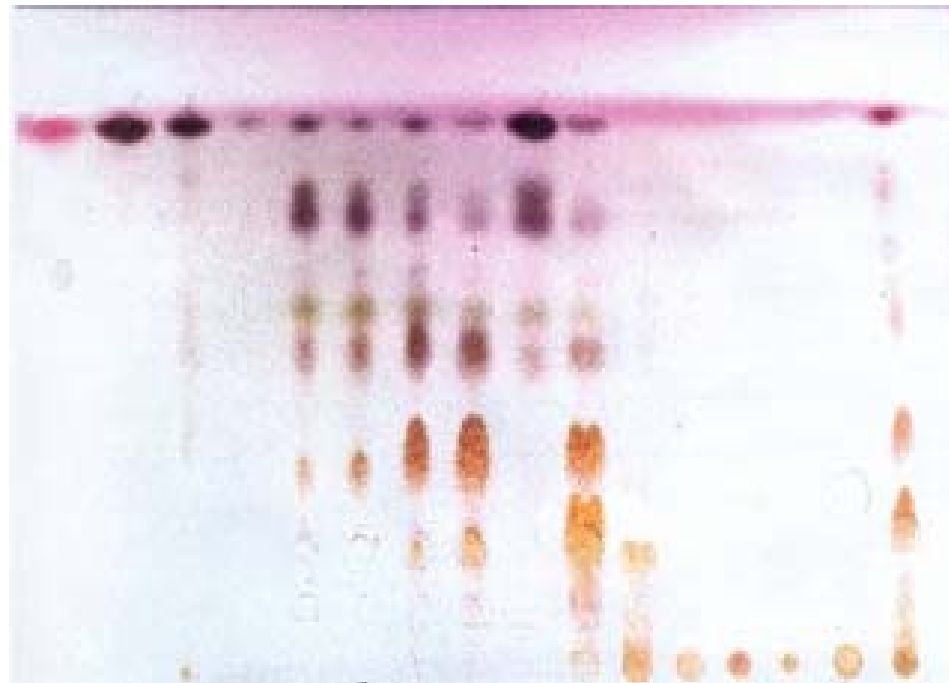
Note for Guidance: Quality of Herbal Medicinal Products

- ▶ “Since the herbal drug/preparation in its entirety is regarded as the active substance, a mere determination of the stability of the constituents with known therapeutic activity will not suffice.”
- ▶ “It must be shown, as far as possible eg. by means of appropriate fingerprint chromatograms, that other substances present in the herbal drug or in the herbal drug preparation are likewise stable and that their proportional content remains constant.”

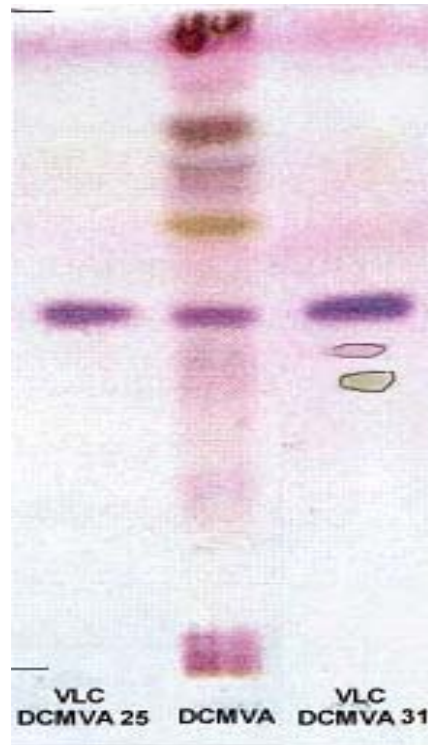
Note for Guidance: Quality of Herbal Medicinal Products

“If a HMP contains several herbal drugs/ preparations and if it is not possible to determine the stability of each active substance, the stability of the medicinal product should be determined by appropriate fingerprint chromatograms, appropriate overall methods of assay and physical and sensory tests or other appropriate tests.”

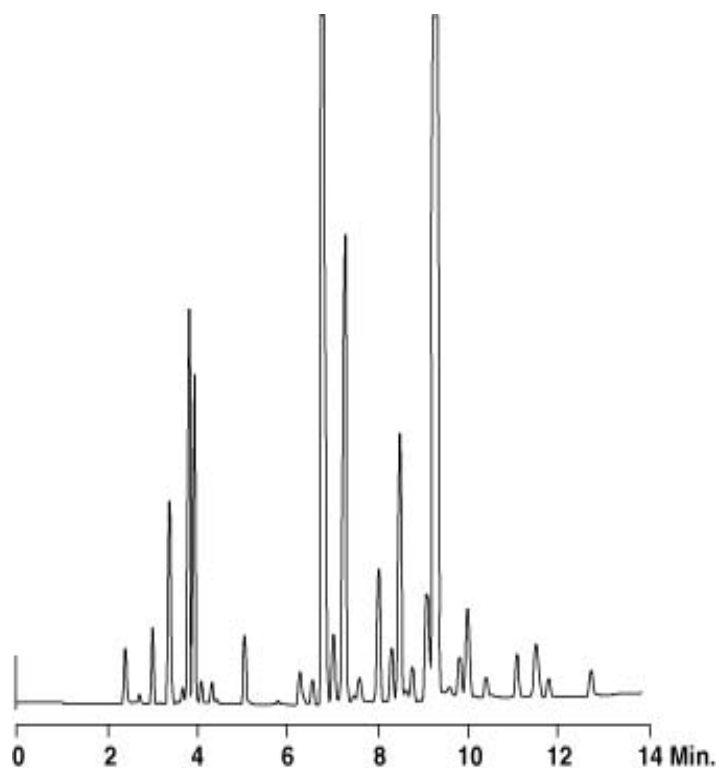
TLC Fingerprint Chromatogram



TLC Fingerprint Chromatogram



HPLC Fingerprint Chromatogram



Note for Guidance: Quality of Herbal Medicinal Products

“In the case of a HMP with constituents of known therapeutic activity the variation during the shelf-life should not exceed $\pm 5\%$ of initial assay, unless justified.”

Nfg: Specifications: Test Procedures and Acceptance Criteria for Herbal Drugs/ Preparations and HMPS

- ▶ “due to the inherent complexity of herbal products there may be no single stability-indicating assay or parameter that profiles the stability characteristics.”
- ▶ may require a series of product-specific, stability-indicating tests
- ▶ ‘case by case’ basis depending on the herbal ingredients and complexity of the product

Traditional Herbal Medicinal Products

Registration Dossier Requirements
November 2004



Conclusions

- ▶ an introduction and early guidance to potential applicants on the registration dossier – **provided**
- ▶ a look at the dossier from ‘top to toe’ – **done**
- ▶ focus on herbal products – **most definitely**

Next Steps

- ▶ to complete our first round of meetings with potential applicants
- ▶ to develop and a deliver a future programme of seminars
- ▶ to ensure web-site provides most up-to-date guidance