BfArM
Federal Institute for Drugs and Medical Devices

Traditional Herbal Medicinal Products

Registration of traditional herbal medicinal products
applicable to ***traditional*** herbal medicinal products

Article 16c 1 (c)

> 30 years of medicinal use within the EU or

> 15 years in and > 15 years outside the EU

Deviations may be decided by the
Herbal Medicinal Products Committee (HMPC, EMEA)
if requested by a Member State

BfArM
Federal Institute for Drugs and Medical Devices

Access to the Market - Options

Marketing authorisation

full, bibliographic or hybrid application

Registration

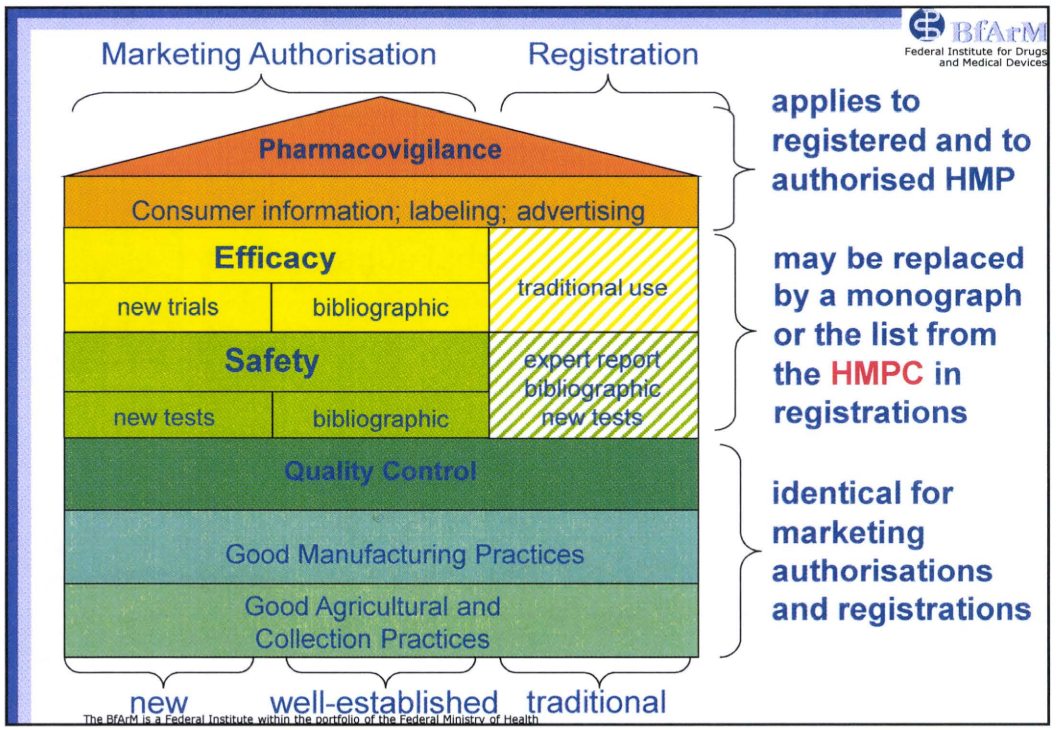
(simplified with respect to the proof of efficacy)

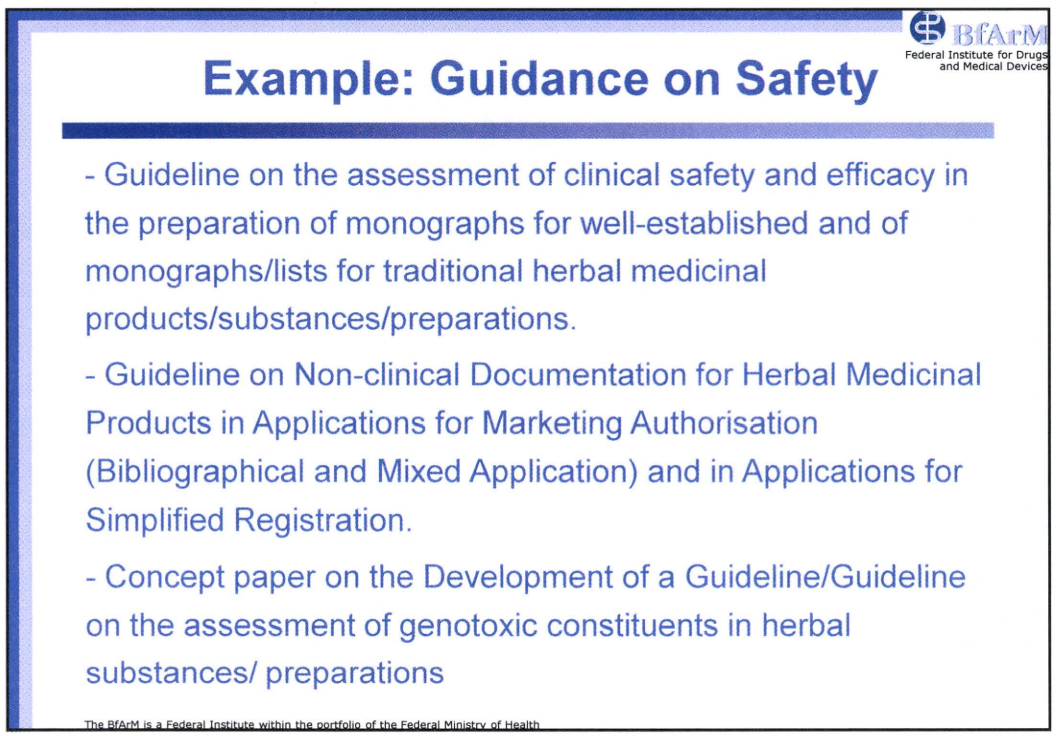
Procedures: national, *MRP, DCP, CP*

Individual prescriptions

"Magistral formula"

The BfArM is a Federal Institute within the portfolio of the Federal Ministry of Health


Marketing Authorisation
Registration
Pharmacovigilance
Consumer information; labeling; advertising
Efficacy
new trials
bibliographic
traditional use
Safety
new tests
bibliographic
expert report
bibliographic
new tests
Quality Control
Good Manufacturing Practices
Good Agricultural and Collection Practices
new
well-established
traditional
applies to registered and to authorised HMP
may be replaced by a monograph or the list from the HMPC in registrations
identical for marketing authorisations and registrations
BfArM
Federal Institute for Drugs and Medical Devices
The BfArM is a Federal Institute within the portfolio of the Federal Ministry of Health


Example: Guidance on Safety
- Guideline on the assessment of clinical safety and efficacy in the preparation of monographs for well-established and of monographs/lists for traditional herbal medicinal products/substances/preparations.
- Guideline on Non-clinical Documentation for Herbal Medicinal Products in Applications for Marketing Authorisation (Bibliographical and Mixed Application) and in Applications for Simplified Registration.
- Concept paper on the Development of a Guideline/Guideline on the assessment of genotoxic constituents in herbal substances/ preparations
BfArM
Federal Institute for Drugs and Medical Devices
The BfArM is a Federal Institute within the portfolio of the Federal Ministry of Health

BfArM
Federal Institute for Drugs and Medical Devices

(Traditional) Herbal Medicinal Products

Medicinal plant

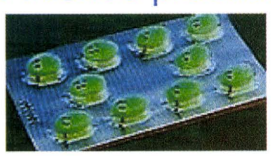
Herbal substance

Herbal preparation

GACP

GMP

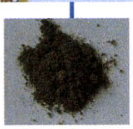
Finished product

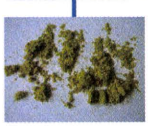


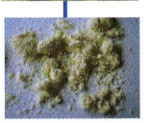
Defined by manufacturing process and specifications

BfArM
Federal Institute for Drugs and Medical Devices

Combination Products



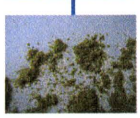




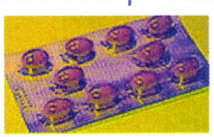
Medicinal plants

Herbal substances

Herbal preparations



Finished product



The BfArM is a Federal Institute within the portfolio of the Federal Ministry of Health

BfArM
Federal Institute for Drugs and Medical Devices

Quality Guidance

Guideline on Quality of Herbal Medicinal Products/ Traditional Herbal Medicinal Products (CPMP/QWP/2819/00 Rev. 1)

Guideline on Specifications: Test procedures and Acceptance Criteria for Herbal Drugs, Herbal Drug Preparations and Herbal Medicinal Products/Traditional Herbal Medicinal Products (CPMP/QWP/2820/00 Rev. 1)

Guideline on Quality of Combination Herbal Medicinal Products/Traditional Herbal Medicinal Products (EMEA/HMPC/CHMP/CVMP/214869/2006)

Guideline on Good Agricultural and Collection Practice (GACP) for Starting Materials of Herbal Origin (EMEA/HMPC/246816/2005)

Guideline on Declaration of Herbal Substances and Herbal Preparations in Herbal Medicinal Products/ Traditional Herbal Medicinal Products in the SPC" (EMEA/HMPC/287539/2005)

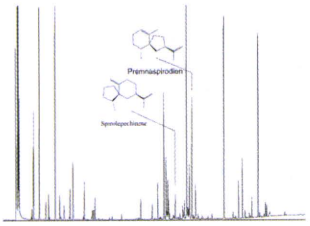
BfArM
Federal Institute for Drugs and Medical Devices

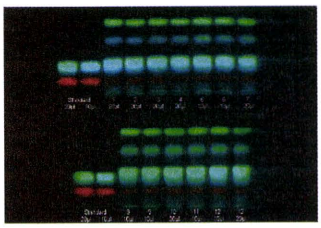
European Pharmacopeia

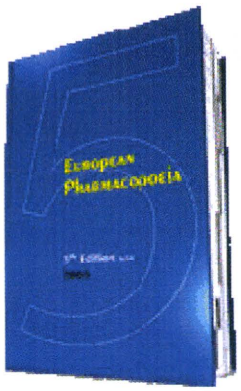
The BfArM is a Federal Institute within the portfolio of the Federal Ministry of Health

BfArM
Federal Institute for Drugs and Medical Devices

European Directory for the Quality of Medicines - EDQM







European Pharmacopeia, Strasbourg

Monographs on quality of

herbal substances and preparations

BfArM
Federal Institute for Drugs and Medical Devices

Extracts - classification

Standardised extracts
- adjusting the herbal substance/preparation to a defined content of a constituent or a group of constituents with known therapeutic activity
- by adding excipients or by blending batches of the herbal substance and/or herbal preparation

Quantified extracts
- adjusting the herbal substance or herbal preparation to a defined range of constituents (active markers)
- by blending different batches of herbal substances and/or herbal preparations

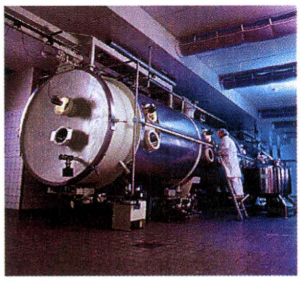
Other extracts
- active substances for which neither constituents with known therapeutic activity nor active markers are known
- not adjusted to a defined content of analytical marker

BfArM
Federal Institute for Drugs and Medical Devices

Manufacturing process

Defined and documented manufacturing process

- GACP
- GMP



BfArM
Federal Institute for Drugs and Medical Devices

Production

- Guideline on Good Agricultural and Collection Practice (GACP) for Starting Materials of Herbal Origin (EMA/HMPC/246816/2005)
- EUDRALEX: Volume 4 Medicinal Products for Human and Veterinary Use:
  Good Manufacturing Practice - Annex 7:
  Manufacture of Herbal Medicinal Products

BfArM
Federal Institute for Drugs and Medical Devices

Good Agricultural and Collection Practice

- Introduction
- General
- Quality Assurance
- Personnel Education
- Buildings and Facilities
- Equipment
- Documentation
- Seeds and Propagation Material
- Cultivation
- Collection
- Harvest
- Primary Processing
- Packaging
- Storage and Distribution

Approach: Realisation of a quality assurance
Minimum of contamination/adversely affecting

BfArM
Federal Institute for Drugs and Medical Devices

Good Agricultural and Collection Practice

1. Introduction:

- „In the case of herbal preparations the production and primary processing of the medicinal plant/herbal substance has a direct influence on the quality of the API"

The following Guideline on good agricultural and collection practice **does not fall directly under GMP-guidelines in the traditional sense**. However, these considerations should be used as a basis for the establishment of such an appropiate quality assurance system.

2. General:

- …These consideration **should be read in connection with GMP guidelines for API** …
- Growers and collectors of medicinal plants/herbal substances must ensure that they avoid damage to existing wildlife habitats (CITES – Convention on International Trade in Endangered species of Wild Fauna and Flora).

3. Quality Assurance:

- Agreements between producers and buyers of medicinal plants/herbal substances with regards to quality … must be based on recognised regional and/or national specifications and should be laid down in written form

The BfArM is a Federal Institute within the portfolio of the Federal Ministry of Health

BfArM
Federal Institute for Drugs and Medical Devices

Harvest

BfArM
Federal Institute for Drugs and Medical Devices

Primary Processing

„Primary processing includes washing, cutting before drying, fumigation, freezing, distillation, drying, etc. Where applicable, all of these processes must conform to regional/or national regulation and **should be carried out as soon after harvesting as possible**“

On arrival at the processing facility the harvestet medicinal plant/herbal substance has to be promptly unloaded and unpacked. …

The BfArM is a Federal Institute within the portfolio of the Federal Ministry of Health

BfArM
Federal Institute for Drugs and Medical Devices

Packaging and Storage

BfArM
Federal Institute for Drugs and Medical Devices

Conclusions (1)

- There is a clear regulatory framework for (traditional) herbal medicinal products in the European Union.
- Currently, different traditions in the Member States are being harmonised by the work of MLWP and HMPC. Community monographs (safety, efficacy) are established.
- GACP is applied by the manufacturers and the concept is assessed in applications for licensing.
- EDQM monograph + HMPC monograph
  = standards for licensing

The BfArM is a Federal Institute within the portfolio of the Federal Ministry of Health

BfArM
Federal Institute for Drugs and Medical Devices

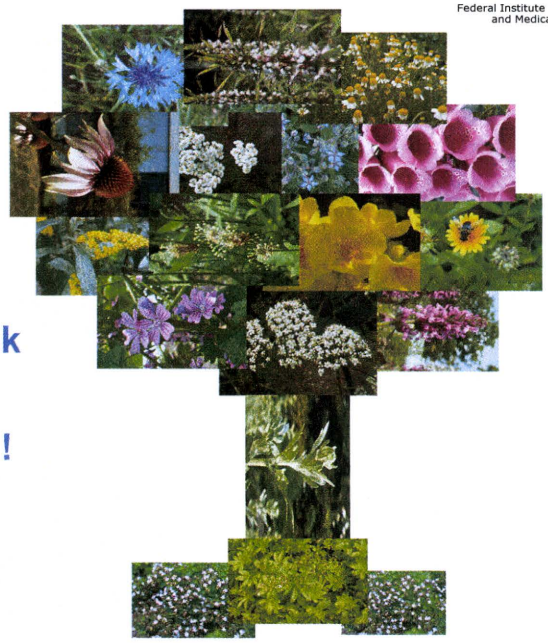
Conclusions (2)

- There is a need for global harmonisation for products which are distributed worldwide.
- Harmonisation of quality is challenging, but realistic.
- Transfer of indications between therapeutic systems should be based on communication and mutual understanding.
- Involvement of health care practitioners of different therapeutic systems is a major challenge for adaptation to existing regulatory frameworks.

BfArM
Federal Institute for Drugs and Medical Devices

Thank

You !



The BfArM is a Federal Institute within the portfolio of the Federal Ministry of Health

Standardization of Traditional Medicine
Toyama, Japan
Nov. 17-18, 2010

Quality Control of Brazilian Phytoremedies

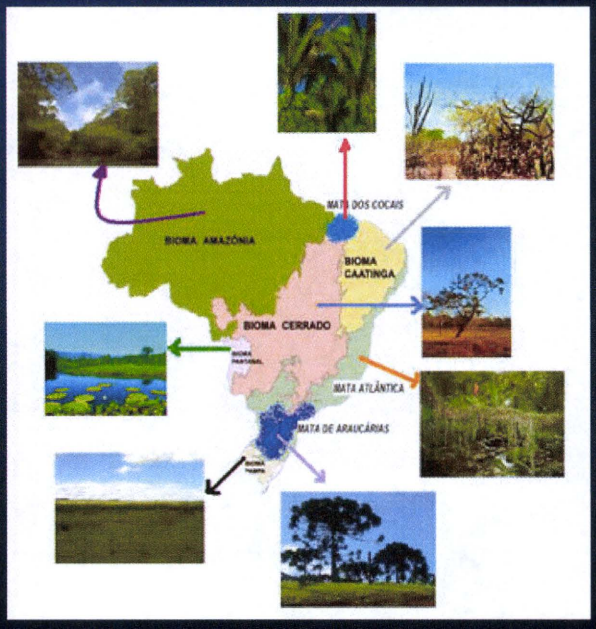
Antonio José Lapa MD, PhD
Mirtes Midori Tanae Pharm, PhD

Natural Products Section – Dept. Pharmacology
Escola Paulista de Medicina / UNIFESP
São Paulo, SP

Pharmacology and Safety Control
Centro de Biotecnologia da Amazônia – CBA

ajlapa@unifesp.br

CBA



BIOMES in BRAZIL
Total Area = 8.514.877 km²

Amazônia	4.196.943	49,3 %
Cerrado	2.036.448	23,9 %
Mata Atlântica	1.110.182	13,0 %
Caatinga	844.453	9,9 %
Pampa	176.496	2,1 %
Pantanal	150.355	1,8 %

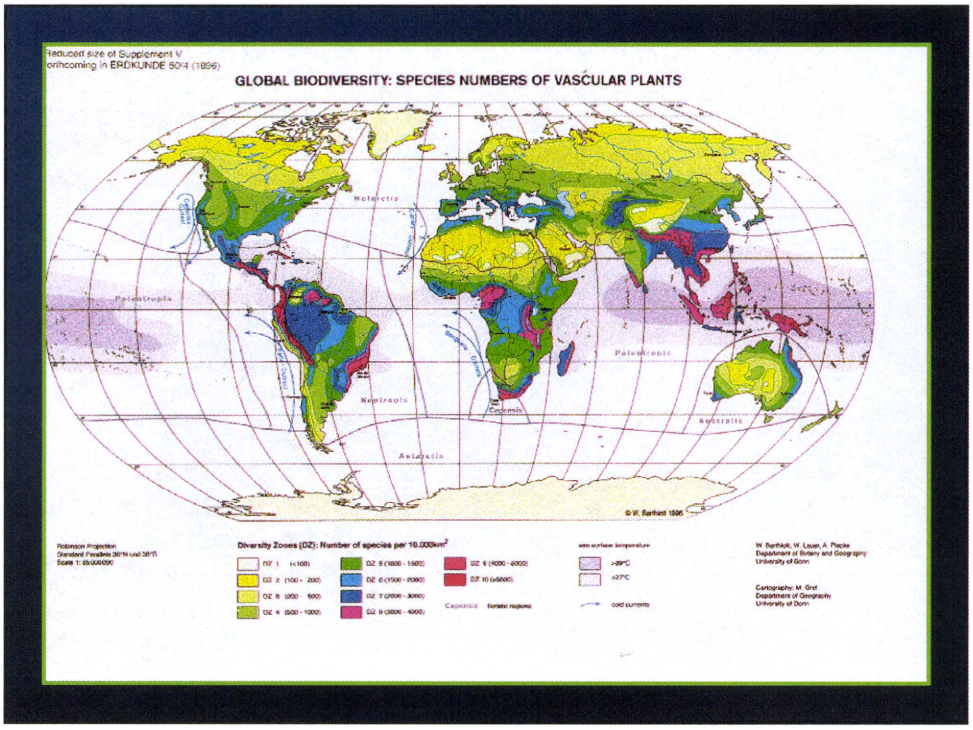
Permanent
Environment
Challenge

100% humidity

Endophytic
Microorganisms

"Endophytes are an outstanding source of small molecules"

Atlantic Forest



Caatinga, bioma tipicamente brasileiro

Caatinga

Dry season

Cerrado

Semi-arid

pampa

Natural Products from Endophytic Fungi

M. B. C. Gallo, D. O. Guimarães, L. S. Momesso, M. T. Pupo*

www.biota.org.br/publi/banco/docs/1091_1199794781.doc

A Review

Symbiosis between a fungus and a plant is a widespread phenomenon in nature, which has been prevalent, ancient, evolutionary consequential in promoting diversity, and plays a major role in structuring plant communities by affecting colonization, competition, coexistence and soil nutrients dynamics (Pyrozynski and Hawksworth, 1998; Clay and Holah, 1999; Lemons *et al.*, 2005).

Natural Products from Endophytic Fungi
M. B. C. Gallo, D. O. Guimarães, L. da S. Momesso, M. T. Pupo*
www.biota.org.br/publi/banco/docs/1091_1199794781.doc

Symbiosis between a fungus and a plant is a widespread phenomenon in nature, which has been prevalent, ancient, evolutionary consequential in promoting diversity, and plays a major role in structuring plant communities by affecting colonization, competition, coexistence and soil nutrients dynamics (Pyrozynski and Hawksworth, 1998; Clay and Holah, 1999; Lemons *et al.*, 2005).

As a result of these long-held interactions, it is feasible to arouse that some endophytic microbes may have devised genetic systems allowing for transfer of information between themselves and the host plant.

As a consequence, the associated microorganisms can learn as much as teach biochemical pathways in order to produce substances common to their hosts or *vice versa* that may have application outside the host plant in which they normally reside (Strobel, 2002).

Natural Products from Endophytic Fungi

M.B. C. Gallo, D. O. Guimarães, L. S. Momesso, M. T. Pupo*

www.biota.org.br/publi/banco/docs/1091_1199794781.doc

Symbiosis between a fungus and a plant is a widespread phenomenon in nature, which has been prevalent, ancient, evolutionary consequential in promoting diversity, and plays a major role in structuring plant communities by affecting colonization, competition, coexistence and soil nutrients dynamics (Pyrozynski and Hawksworth, 1998; Clay and Holah, 1999; Lemons *et al.*, 2005).
As a result of these long-held interactions, it is feasible to arouse that some endophytic microbes may have devised genetic systems for transfer of information between themselves and the host plant.
As a consequence, the associated microorganisms can learn as much as teach biochemical pathways in order to produce substances common to their hosts or *vice versa* that may have application outside the host plant in which they normally reside (Strobel, 2002).

Plant-derived anticancer drugs have also been identified from endophytic fungal cultures. Paclitaxel (Taxol®) (3), for breast and ovarian cancers, was isolated from *Taxomyces andreanae*, an endophytic fungus associated with the Pacific yew *Taxus brevifolia* (Stierle *et al.*, 1993).

An endophytic fungus from leaves of *Catharanthus roseus* biosynthesize the potent antileukemia agent vincristine (4) (Yang *et al.*, 2004).

Natural Products from Endophytic Fungi

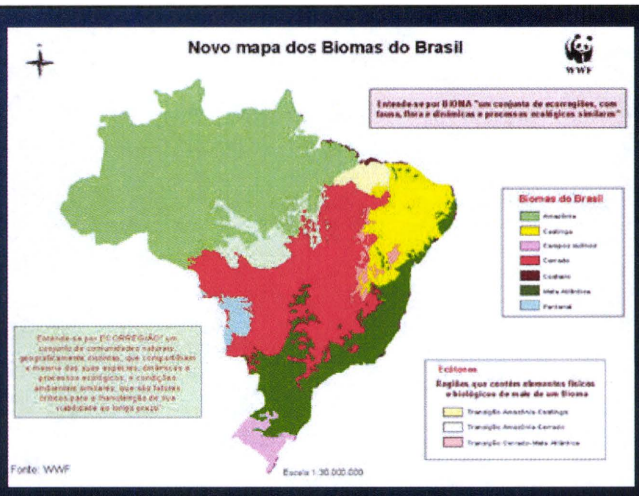
M. B. C. Gallo, D. O. Guimarães, L. S. Momesso, M. T. Pupo*

www.biota.org.br/publi/banco/docs/1091_1199794781.doc

Symbiosis between a fungus and a plant is a widespread phenomenon in nature, which has been prevalent, ancient, evolutionary consequential in promoting diversity, and plays a major role in structuring plant communities by affecting colonization, competition, coexistence and soil nutrients dynamics (Pyrozynski and Hawksworth, 1998; Clay and Holah, 1999; Lemons *et al.*, 2005).
As a result of these long-held interactions, it is feasible to arouse that some endophytic microbes may have devised genetic systems for transfer of information between themselves and the host plant.
As a consequence, the associated microorganisms can learn as much as teach biochemical pathways in order to produce substances common to their hosts or *vice versa* that may have application outside the host plant in which they normally reside (Strobel, 2002).
Plant-derived anticancer drugs from endophytic fungal cultures.
Paclitaxel (Taxol®) (3), for breast and ovarian cancers, from *Taxomyces andreanae*, associated with *Taxus brevifolia* (Stierle *et al.*, 1993).
An endophytic fungus from *Catharanthus roseus* biosynthesize vincristine (4) (Yang *et al.*, 2004).

Entrophospora infrequens from *Nothapodytes foetida* (Icacinaceae), to produce camptothecin (5) (Puri *et al.*, 2005) (Amna *et al.*, 2006).

Podophyllotoxin (6), precursor of useful anticancer agents, synthesized by *Trametes hirsute*, (Puri *et al.*, 2006).



Therefore, taxonomic identification of the raw material might be insufficient to scale up phytotherapeutic agents!
Chemical standardization + *in vivo* efficacy + bioavailability + (safety ?), as preconized for any other xenobiotic.

Why Investing in New Medicines ?

1 . INNOVATION
- ✓ Higher Therapeutic Index (Safety)
- ✓ Greater Specificity
- ✓ Improved Bioavailability
- ✓ New Pharmacological Spectrum

2. SOCIOECONOMICAL CONTRIBUTION
- ✓ Low costs
- ✓ Availability
- ✓ Competitivity

3. COMPLIANCE

Finding new drug targets in the 21st century

- **Mark A. Lindsay**

Biopharmaceutics Research Group, Airway Disease, National Heart and Lung Institute, Dovehouse Street, Imperial College, London SW3 6LY, UK

Drug Discovery Today 10:1683-1687 (2005)

- Available online 22 December 2005.

The past 30 years have witnessed a steady decline in the number of new drug targets. This review concentrates on the initial process of target identification and argues that current problems have resulted from a decrease in clinical research, an overemphasis on the discovery of new targets through an understanding of the molecular causes of disease and the adoption of cell and animal models that are poor predictors of human disease. To resolve this situation, we argue for increased clinical research and show that an intervention at the physiological level, using drugs to target at the extracellular signalling pathways, will facilitate identification of novel drug targets in the 21st century.

- Finding new drug targets will require a reorientation from the present emphasis upon understanding of the mechanistic and genetic basis of disease to one that is centred upon a more clinical and physiological approach .

- **Author Keywords:** Target identification; validation; drug discovery; reductionism; animal models
- **Subject-index terms:** Pharmaceutical Science; Drug Discovery; Molecular Medicine

INNOVATION OR STAGNATION

CHALLENGE AND OPPORTUNITY ON THE CRITICAL PATH TO NEW MEDICAL PRODUCTS

FDA

US Department of Health and Human Services
Food and Drug Administration
March 2004

http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html 06/22/2004

INNOVATION OR STAGNATION (FDA's)

This report provides the Food and Drug Administration's (FDA's) analysis of the pipeline problem -- the recent slowdown, instead of the expected acceleration, in innovative medical therapies reaching patients.

INNOVATION OR STAGNATION (FDA's)

This report provides the Food and Drug Administration's (FDA's) analysis of the pipeline problem -- the recent slowdown, instead of the expected acceleration, in innovative medical therapies reaching patients.

What is the problem? In FDA's view, the applied sciences needed for medical product development have not kept pace with the tremendous advances in the basic sciences.

INNOVATION OR STAGNATION (FDA's)

This report provides the Food and Drug Administration's (FDA's) analysis of the pipeline problem -- the recent slowdown, instead of the expected acceleration, in innovative medical therapies reaching patients.

What is the problem? In FDA's view, the applied sciences needed for medical product development have not kept pace with the tremendous advances in the basic sciences.

As a result, the vast majority of investigational products that enter clinical trials fail.