Tibetan Herbal Formulas from the Perspective of Western Medicine

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PADMA Inc. Switzerland
www.padma.ch
Content

- Short portrait of PADMA Inc.
- Status of herbal preparations (CH & EU)
- Development in Europe
- Requirements for medicinal products
- Regulatory requirements THMP
- Relevance and kinds of research
- GMP Production
- Research results examples
  Padma 28 and Padma Digestin
- Summary
Padma Inc. Switzerland

Founded: 1969
Co-workers: 35
Location:
  • Production
  • QA-Laboratory
  • Administration

Products: Herbal medicines based on Tibetan Medicine
Tibetan Formulas in Europe
The journey to Switzerland
<table>
<thead>
<tr>
<th>Indikation</th>
<th>Morgens</th>
<th>Mittags</th>
<th>Abends</th>
</tr>
</thead>
<tbody>
<tr>
<td>Claudicatio intermittens</td>
<td>28</td>
<td>28</td>
<td>(179)</td>
</tr>
<tr>
<td>(oder)</td>
<td>28 + 173</td>
<td>137 + 151</td>
<td>(179)</td>
</tr>
<tr>
<td>Colitis</td>
<td>28</td>
<td>115</td>
<td>(179)</td>
</tr>
<tr>
<td>(oder)</td>
<td>28 + 115</td>
<td>151 + 170</td>
<td>(179)</td>
</tr>
<tr>
<td>Colitis ulcerosa</td>
<td>28 + 115</td>
<td>151 + 170</td>
<td>(179)</td>
</tr>
<tr>
<td>Colon - Atonie</td>
<td>(179)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon irritabile</td>
<td>28 + 115</td>
<td>151 + 170</td>
<td>(179)</td>
</tr>
<tr>
<td>mit Ulcus duodeni</td>
<td>115 + 137</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Swiss beginnings: 1965**

Uebersicht über die Indikationen

Wirkungskrachteristik

Rezept-No.

28
(trocken)

Antibakteriell; desinfizierend; regenerierend
Gefäße und Bronchiolen dilatierend
Herz und Kreislauf stimulierend;
Beschleunigt die Heilungsprozesse
Our goal
Tibetan herbal formulas for patients, doctors and therapists in western countries
Our approach

- Marketable product without losing the essence

- Industrial production according to western standards (GMP)
- Research: proof of efficacy to western trained professionals
- National regulatory frameworks, political environment

Tibetan herbal formulas
New packaging machine (blistering, cartoning)

Inauguration by Lama Kunsang (Kreuzlingen CH) Dec 2014
PADMA Products in Switzerland

based on Gabur 25 since 1977

based on Zhi byed 6 since 1970

Se 'bru 5 since 2011

regional registration since 2000
<table>
<thead>
<tr>
<th>Country</th>
<th>Padma Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Switzerland*</td>
<td>PADMA 28, DIGESTIN, Leber-Regulans, LAX, Magenbrennen-Formel, Nerven-Tonikum, Venen-Tonikum</td>
</tr>
<tr>
<td>Denmark</td>
<td>PADMA PLUS</td>
</tr>
<tr>
<td>Hungary</td>
<td>PADMA BASIC</td>
</tr>
<tr>
<td>Italy</td>
<td>PADMA PLUS, DIGESTIN, HEPATEN, ACIBEN</td>
</tr>
<tr>
<td>Latvia</td>
<td>PADMA DIGESTIN, HEPATEN, NERVOTONIN</td>
</tr>
<tr>
<td>Lithuania</td>
<td>PADMA DIGESTIN, HEPATEN, NERVOTONIN</td>
</tr>
<tr>
<td>Netherlands</td>
<td>PADMA BASIC, DIGESTIN, HEPATEN, ACIBEN, NERVOTONIN, VENABEN</td>
</tr>
<tr>
<td>Austria</td>
<td>PADMA DIGESTIN, HEPATEN, NERVOTONIN</td>
</tr>
<tr>
<td>Poland</td>
<td>PADMA BASIC, DIGESTIN, HEPATEN</td>
</tr>
<tr>
<td>UK</td>
<td>PADMA CIRCOSAN</td>
</tr>
<tr>
<td>USA/CAN</td>
<td>PADMA BASIC</td>
</tr>
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Traditional and complementary medicine in Europe

conventional medicine
orthodox medicine
allopathic medicine
biomedical medicine

complementary and alternative medicine
CAM
Traditional and complementary medicine in Europe
Traditional and complementary medicine in Europe

Phytotherapy

- traditional medicine systems (Asian and others)
- manual therapies, exercise
- mind based methods
- acupuncture

homeopathy

anthroposophy
Traditional and complementary medicine in Europe
Traditional and complementary medicine in Europe

TCM
Ayurveda
European Medicine Traditions
Thai Medicine
Tibetan Medicine
American Indian Medicine
Japanese Kampo Medicine
other traditional medicines
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Development in Europe

Interest in complementary and alternative treatment options by patients

Prevalence of complex chronic diseases, multimorbidity (due to age structure and lifestyle)

Regulatory possibilities, market access
<table>
<thead>
<tr>
<th><strong>Categories for herbal products Europe</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>medicines</strong></td>
</tr>
<tr>
<td>in illness, for patients</td>
</tr>
<tr>
<td>indication e.g.:</td>
</tr>
<tr>
<td>'for the use in digestive disorders'</td>
</tr>
<tr>
<td>proove</td>
</tr>
<tr>
<td>• quality</td>
</tr>
<tr>
<td>• safety</td>
</tr>
<tr>
<td>• effectiveness</td>
</tr>
<tr>
<td>status: Traditional herbal medicinal product THMP</td>
</tr>
<tr>
<td><strong>food supplements</strong></td>
</tr>
<tr>
<td>in health, for customers</td>
</tr>
<tr>
<td>no indication, e.g.:</td>
</tr>
<tr>
<td>'improves digestion / supports a healthy digestion'</td>
</tr>
<tr>
<td>show</td>
</tr>
<tr>
<td>• suitability for food</td>
</tr>
<tr>
<td>(non toxicity, lists)</td>
</tr>
<tr>
<td>• plausibility for field of use</td>
</tr>
</tbody>
</table>
Padma international

- Medicinal product
- Food supplement
MP vs. FS: The example Se 'bru 5 in Europe

**medicine**

Padma Digestin CH (THMP)

…is traditionally used when digestion tends to be poor or when there are digestive disorders, as manifested by feelings of pressure or fullness in the stomach area, or flatulence.

**food supplement**

Padma Digestin AT and others

…is an herbal product for the support of a healthy and balanced digestive system. The herbs contained in PADMA DIGESTIN support stomach health and contribute to maintain the digestive system in a healthy and balanced condition.
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From medical tradition to traditional medicine: A Tibetan formula in the European framework

Herbert Schwabl*, Cécile Vennos

Padma AG, Unterfeldstrasse 1, 8340 Hinwil, Switzerland

**ABSTRACT**

**Ethnopharmacological relevance:** The increasing prevalence of complex multi-factorial chronic diseases and multimorbidity reveals the need for an enlargement of the therapeutic options. Potent multi-compound herbal formulations from traditional medicine systems such as Tibetan Medicine might meet the requirements. With its practice over the centuries Tibetan Medicine is one of the important medical heritages of the world. In the 20th century Tibetan formulas came to Switzerland, where the formula
From medical tradition to traditional medicine

Solidification and reduction process

Traditional formula

Solidification

Quality

Indication
From medical tradition to traditional medicine

Choose formula regarding:

- Suitable ingredients
  (safety, availability on world market, species protection, …)
- Suitable field of application
- OTC suitability
- Efficacy
- Market analysis, competitor products
From medical tradition to traditional medicine

Exact definition:

- Identity of components
- Exact composition
- Excipients
- Galenic form

Illustration showing the process from traditional formula to solidification, quality, indication, and finally product form.
From medical tradition to traditional medicine

Quality:

- Develop quality concept (analytical development)
- Chemical markers?
- Validated analytic methods?
- Consult international guidelines for requirements, e.g. ‘combination guideline’

[EU Guideline on quality of combination herbal medicinal products & traditional herbal medicinal products (EMEA/HMPC/CHMP/CVMP/214869/2006)]
From medical tradition to traditional medicine

**Indication:**

Define an indication in Western medical terms with regard to

- Traditional field of application
- Suitability to THMP and to OTC distribution
- Marketability

[EU Guideline on quality of combination herbal medicinal products I traditional herbal medicinal products (EMEA/HMPC/CHMP/CVMP/214869/2006)]
Indication?

E.g. the formula Padma 28 (Padma Basic, Padma Circosan)

**Characteristics from a TM traditional point of view**

- Based on Gabur 25
- increases rLung principle
- lowers Tripa in circulatory system
- cooling, mobilizing formula
- antibacterial, disinfecting, regenerative
- stimulates heart and blood circulation
Swiss beginnings: 1965

<table>
<thead>
<tr>
<th>Rezept-No.</th>
<th>Wirkungscharakteristik</th>
<th>Indikationsbeispiele</th>
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<tr>
<td>28 (trocken)</td>
<td>Antibakteriell; desinfizierend; regenerativ; Gefässe und Bronchien dilatierend; Herz und Kreislauf stimulierend; Beschleunigt die Heilungsprozesse.</td>
<td>Alle akuten und chronischen, rezidivierenden Infektionen; kann auch zur Wundbestreuung verwendet werden. Funkt. und organ., Herz- und Kreislauffkr. Herz- und Kreislaufinsuffizienz; Status nach Luft- und Kreislaufinsuffizienz; Angina pectoris; Claudicatio intermittens;</td>
</tr>
</tbody>
</table>
Indications Padma 28

Fields of use from a traditional western point of view

- acute and chronic inflammation
- recurrent and especially purulent infections
- wound healing
- circulatory disorders
- asthma
- colitis, ulcerative colitis
- tissue defects caused e.g. by skin disorders, venous ulcer, peptic ulcer, myocardial infarction, traumas

Indication (Swiss package insert)

- circulatory disorders with symptoms such as:
  - tingling sensation
  - formication
  - feeling of heaviness and tension in the legs and arms
  - numbness of the hands and feet
  - calf cramps
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Medicines Agencies

Switzerland: swissmedic

EU: European Medicines Agency

and 28 national Medicines Agencies
Medicinal Product dossier
CTD structure (common technical document)

Quality
(GMP manufacturing)

Safety
(non-clinical data)

Efficacy
(clinical trials)
Medicinal Product dossier THMP

Quality (GMP manufacturing)
Safety (non-clinical data)
traditional use

Plausibility of efficacy
Requirements for THMP

- **Quality**
- **Safety**
- **Tradition**: medicinal use over at least 30 years, including at least 15 years within the EU (in the indication and dosage applied for)
- herbal ingredients (ancillary vitamins or minerals allowed)
- specified strength and posology, oral, external and/or inhalation application
- indications for use without the supervision of a medical practitioner (→ OTC)

**Plausibility of efficacy**

- only 'weak' indications, symptom oriented
Example registration Switzerland

Se ‘bru 5

2000    local registration (Ct. AR)
2001-10 in use, no side effects

2006    Start project
2008    hand in registration dossier
2010    registration (kat. C)
2011    Introduction on market

2012    appl. for kat. D (+ drugstores)
2014    approval (court case)
Dossier PADMA DIGESTIN (Se 'bru 5 in CH)

2 people, 5 years:
5 cartons of paper
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Kinds of research

Medicine system Effectiveness

- individualized treatment
- including the whole diagnostic and therapeutic options (e.g. diet, internal and external methods)

Specific formulas/methods effectiveness/activities

- clinical e.g. vs. placebo or vs. active control
- experimental studies
Importance of research regulatory context

Plausibility of efficacy shown by traditional use.

No clinical studies are necessary to prove efficacy.

Nowadays (for THMPs) scientific studies important for marketing purposes / communication with medical professionals.
Our approach

marketable product without losing the essence

- industrial production according to western standards (GMP)
- research: proof of efficacy to western trained professionals
- national regulatory frameworks, political environment

Tibetan herbal formulas
Kinds of research

**Clinical studies**
- Meta-analyses
- RCT randomized controlled trials
- Other studies (open label, case control, etc.)

**Experimental studies**
- Cell free tests
- Cell cultures
- Organ/tissue cultures
- (Animal models)

- Efficacy in a given indication
- Mechanisms, modes of action
Complexity as characteristic

The whole is more than the sum of its parts

some components of Padma 28
Therefore:

- research the whole formula
- research the clinical effects and biochemical mechanisms using modern scientific methods and language
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We need...

A well defined, standardized formula as test substance

Guideline on **Good Manufacturing Practice**
Manufacturing

raw material  milling  mixing

encapsulating
blistering/
packaging

finished product
Manufacturing

raw material  milling  mixing

encapsulating

blistering/
packaging

finished product
Manufacturing

raw material → milling → mixing → encapsulating → blistering/packaging → finished product

Horizontal-Zwangsmischer Diosna H 3200
Manufacturing

raw material  milling  mixing

encapsulating

blistering/
packaging

finished product

Kapselmaschine Bosch GFK 2500
Manufacturing

raw material  milling  mixing

encapsulating

blistering/packaging

finished product
Manufacturing

raw material  milling  mixing  encapsulating  blistering/packaging  finished product
Quality control

- raw material
- powder
- mixture

QC
- identity, quality, purity

QC
- tightness, completeness, labeling

encapsulating

blistering/packaging

finished product

PADMA

GMP
Quality control

1 formula,
21 ingredients
~380 analyses per lot
Purity

external laboratories
e.g. aflatoxins
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**Example Padma 28 (Padma Circosan)**

Clinical studies (total 32)

- Different chronic inflammatory diseases
- Vascular diseases, esp. PAOD

---

**Number of patients in clinical trials with Padma 28 in different indications**

- Juvenile chronic arthritis (1 study): 12 (20 controls)
- HIV infection (1 study): 15 (50 controls)
- Duodenal ulcus (1 study): 23 (49 controls)
- Multiple sclerosis (1 study): 50 (50 controls)
- Lipid metabolic disorders (2 studies): 63 (49 controls)
- Chronic active Hepatitis B (2 studies): 44 (49 controls)
- Chronic recurrent infections in children (6 studies): 245 (224 controls)
- Other vascular diseases (11 studies): 159 (266 controls)
- Intermittent claudication (11 studies): Total 1330 patients

[Vennos et al. Forsch Komplementmed 2013]
PAOD?

Peripheral arterial occlusive disease (atherosclerosis in leg arteries)

diminished blood flow
	pain during walking
Padma 28 in PAOD

Meta-analysis: 5 placebo controlled clinical studies, 272 patient data

Baseline

Placebo
Padma 28

standardized measuring of painfree and maximum walking distance on a treadmill

max. walking distance in meters

[Melzer et al. Atherosclerosis, 2006]
Padma 28 in PAOD

Meta-analysis: 5 placebo controlled clinical studies, 272 patient data

[Melzer et al. Atherosclerosis, 2006]
Anti-inflammatory effect of Padma 28

inhibits cellular inflammation reaction
modulates immune response

inhibits pro-inflammatory cytokine IL-1β (and IL-6, IL-8, TNF-α)

[Barak et al. Eur Cytokine Netw, 2004]
Antiatherogenic properties

Padma 28 inhibits the production of E-selectin (adhesion molecule)

Reduction of immigration of immune cells into the vessel wall

Reduction of vessel wall inflammation (atherosclerosis)

[Exner et al., Forsch Komplementärmed 2006]
Atherosclerosis as network disease

Padma 28: Activity profile (summary)

Padma 28 is:

- anti-inflammatory
- antioxidative
- improves blood circulation
- antibacterial
- immune modulating
- protects cells and proteins from damage and degradation
Padma Digestin in functional dyspepsia

FD definition/diagnosis acc. Rome III criteria.

One or more of the following:

a. Bothersome postprandial fullness
b. Early satiation
c. Epigastric pain
d. Epigastric burning

For at least 3 months, since at least 6 months

AND

No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms

[Rome foundation, www.romecriteria.org]
Padma Digestin in functional dyspepsia

Multicentric, clinical open-label study in patients with FD

Treatment:
2 x 3 capsules Padma Digestin daily during 6 weeks

- patients included: 37  
  (safety data)
- intention to treat (ITT): 31  
  (efficacy)

[Meier et al. Forsch Komplement-med 2013]
Padma Digestin in functional dyspepsia

Number of patients afflicted with the symptom in relevant severity (severe or very severe) before and after Padma Digestin treatment in % (ITT n=31)

Localized epigastric pain*

Lack of appetite*

Diffuse epigastric pain*

Stomach cramps*

Nausea**

Postprandial fullness**

Regurgitation

Diarrhea

Eructation

Vomiting

Heartburn

Fasting/nocturnal pain

Constipation

Early satiety

Bloating

Lower abdominal pain

[Meier et al. Forsch Komplement-med 2013]
Global efficacy rated as good or very good by 84% of the patients and doctors
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The regulatory situation for herbal preparations in western Europe is difficult. Different options for market access are available (e.g. registration as THMP or status food supplement).

With THMP and food supplements as options research is not required. Only for marketing purposes with medical professionals.

Quality and analytical requirements are steadily rising.

Examples show that there are possibilities, but a lot of know-how, perseverance and sometimes creative solutions are necessary.
Summary

Quality and analytical requirements are steadily rising. Examples show that there are possibilities, but a lot of know-how, perseverance and sometimes creative solutions are necessary.

The regulatory situation for herbal preparations in western Europe is difficult. Different options for market access are available (e.g. registration as THMP or status food supplement). With THMP and food supplements as options research is not required. Only for marketing purposes with medical professionals.

It is an uphill struggle... which is not requiring. Without much of know-how are necessary... but we keep on pushing!
Thank you for your attention

Dr. Cécile Vennos
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