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How can natural health products fit into the regulatory shelf of the EU?

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Natural Compounds and Drug Development Day
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Outline

1. Introduction
2. Medicinal Product
3. Food
4. Medical Device
5. Summary

EU Shelf of Natural Health Products

... they are similar but not identical!

… how to handle them best?

dietary supplements

functional foods

food for special medical purposes

OTC

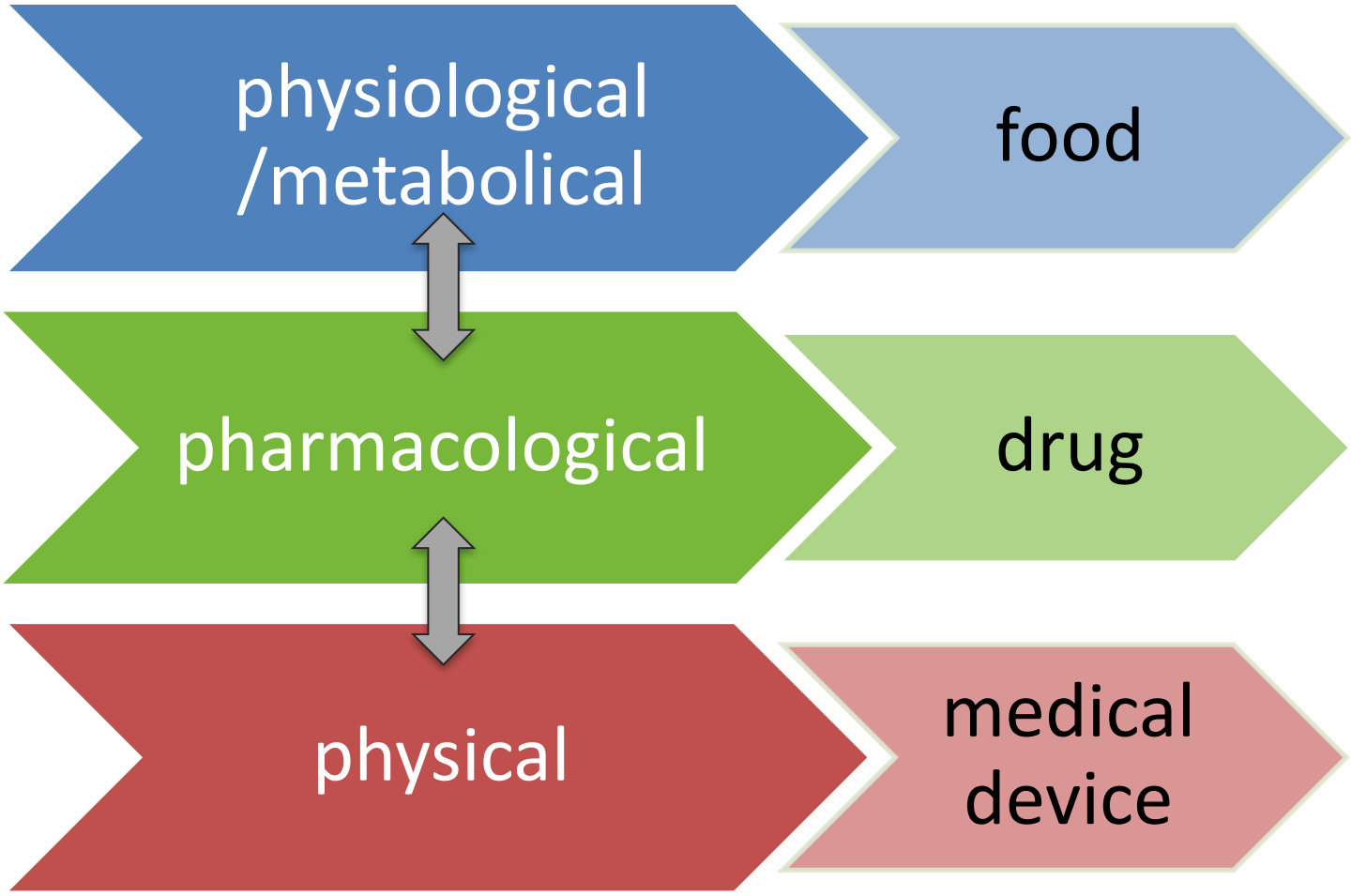
herbal drugs

medical devices

Identification of the right category

✓ **science is key!**	• Knowing the ins and outs of natural compounds • Best interpretation of experimental and clinical results ⇒ Understanding the products
✓ **safety**	• The indispensible basis for all products
✓ **mode of action**	• Determines the regulatory category
✓ **strategy**	• Best claims for best positioning in best category • Finding ways to market for novel and old ingredients

Demarcation by mode of action

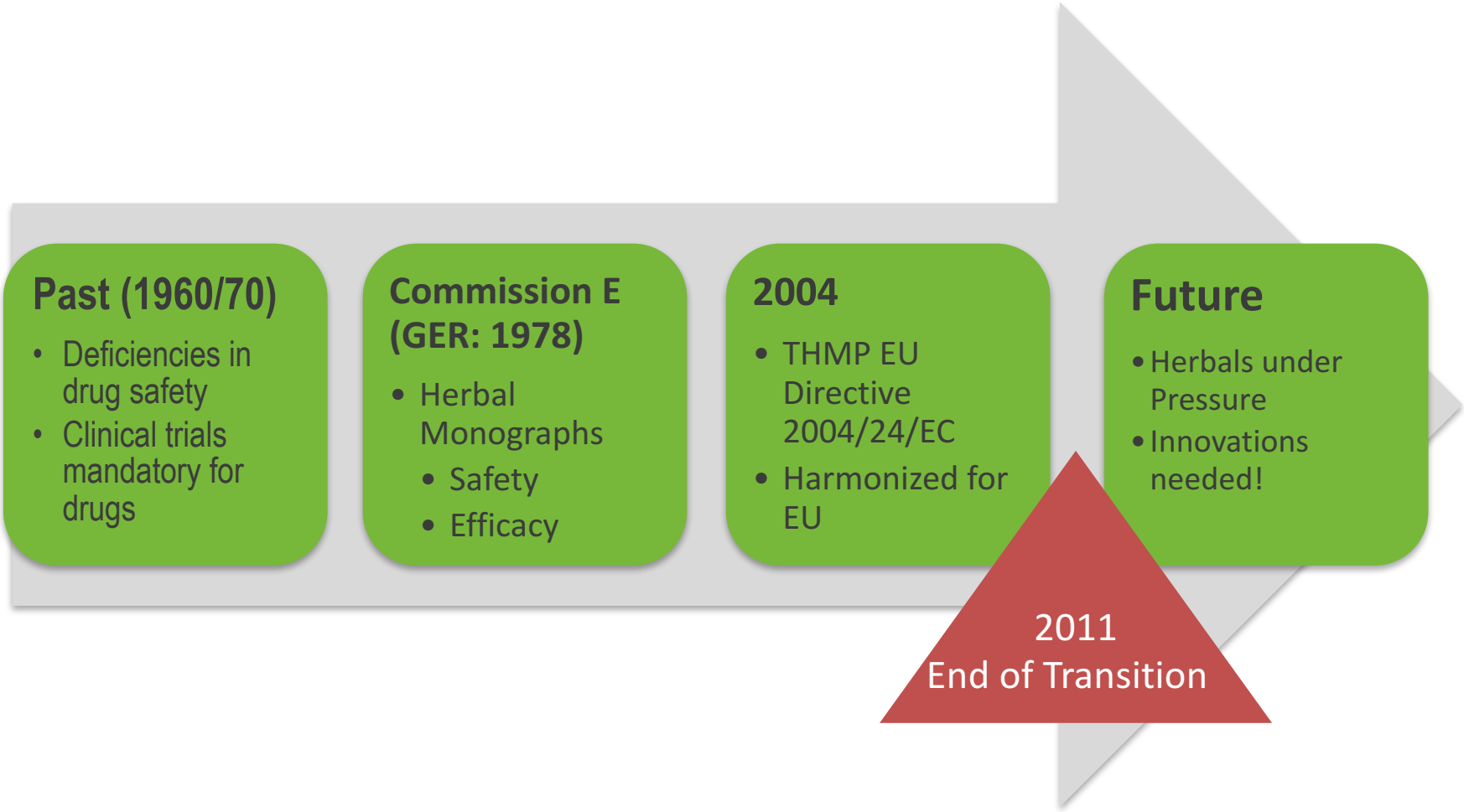


Medical Categories in the EU

- Three main drug categories
  - Full marketing authorization for new drug according Art. 8(3) of Directive 2001/83/EC
  - Well-established use drugs (WEU) according to Art. 10a of Directive 2001/83/EC
  - Traditional Herbal Medicinal Product (THMP) according to THMP Directive 2004/24/EC

- Minor drug categories
  - Orphan Drug (Orphan regulation (EC) No 141/2000)
  - (Homeopathic (Article 14 or 16 of Directive 2001/83/EC)
  - Anthroposophical Therapy (Article 14 or 16 of Directive 2001/83/EC))

History of THMP



THMP – Basic Requirements

- EU Directive 2004/24/EC; *Article 16a* of Directive 2001/83/EC
  - **Proof of a 30 years tradition of safe medical use**
    - 30 years world wide and 15 years of which must be within the EU (*Article 16*a(1)d))
  - The regulation is confined to **herbs only** (possibility to add ancillary quantities of **vitamins or minerals**), no isolated active components
  - Only **oral**, **topical**, or by **inhalation** applied nonprescription drug use
  - Indication: **self diagnosable, w/o medical supervision**
  - **Production/Quality** according GMP

THMP – Proofing the Tradition

- Proof of Tradition replaces clinical studies (CTD module 2.5)

  Most important information:

  - **Time** in safe medicinal use (30 years world wide, thereof 15 EU)
  - Same traditional therapeutic **indication** (self diagnosed, w/o medical supervision)
  - Same **strength/type** of preparation
    - **Important: same (comparable) DER, same extraction solvent**
  - Same **posology** (dosage) and
  - Same **dosage form**

- "Proof of traditional use" by detailed reference to
  - scientific literature
  - best with historically comparable reference product
  - post-marketing data (if available)

THMP – Non-Clinical Requirements

Non-Clinical requirements (CTD module 2.4) = Safety (*Article 16*a(1)e)

- Pharmacological and Toxicological expert statement
  - ***Pharmacology:***
    - No own data: bibliographic
  - ***Pharmacokinetics:***
    - No own data: bibliographic
  - ***Toxicology:***
    - No own data: bibliographic
- A product specific AMES test (genotoxicity) is required
  - Guideline: genotoxicity of herbal substances/preparations' (EMEA/HMPC/107079/2007; EMEA/HMPC/67644/2009; EMEA/HMPC/166326/2005)
  - Further safety tests upon authority request is required

THMP – Requirement on Indication

- Indication has to be self diagnosable, without medical supervision, or to refer to the use ‘after exclusion of serious conditions by a medical doctor’, for more serious pathologic conditions
- Indication is part of the „Proof of Traditional use“

  => Same traditional therapeutic **indication**
- The product labeling: “product x is a Traditional Herbal Medicinal Product, traditionally for the use for indication z, exclusively based on longstanding use.“

THMP – Quality Requirements

QUALITY (Directive 2001/83/EC *Article 16*e(1)e)

- Quality requirements are as high as for any drugs

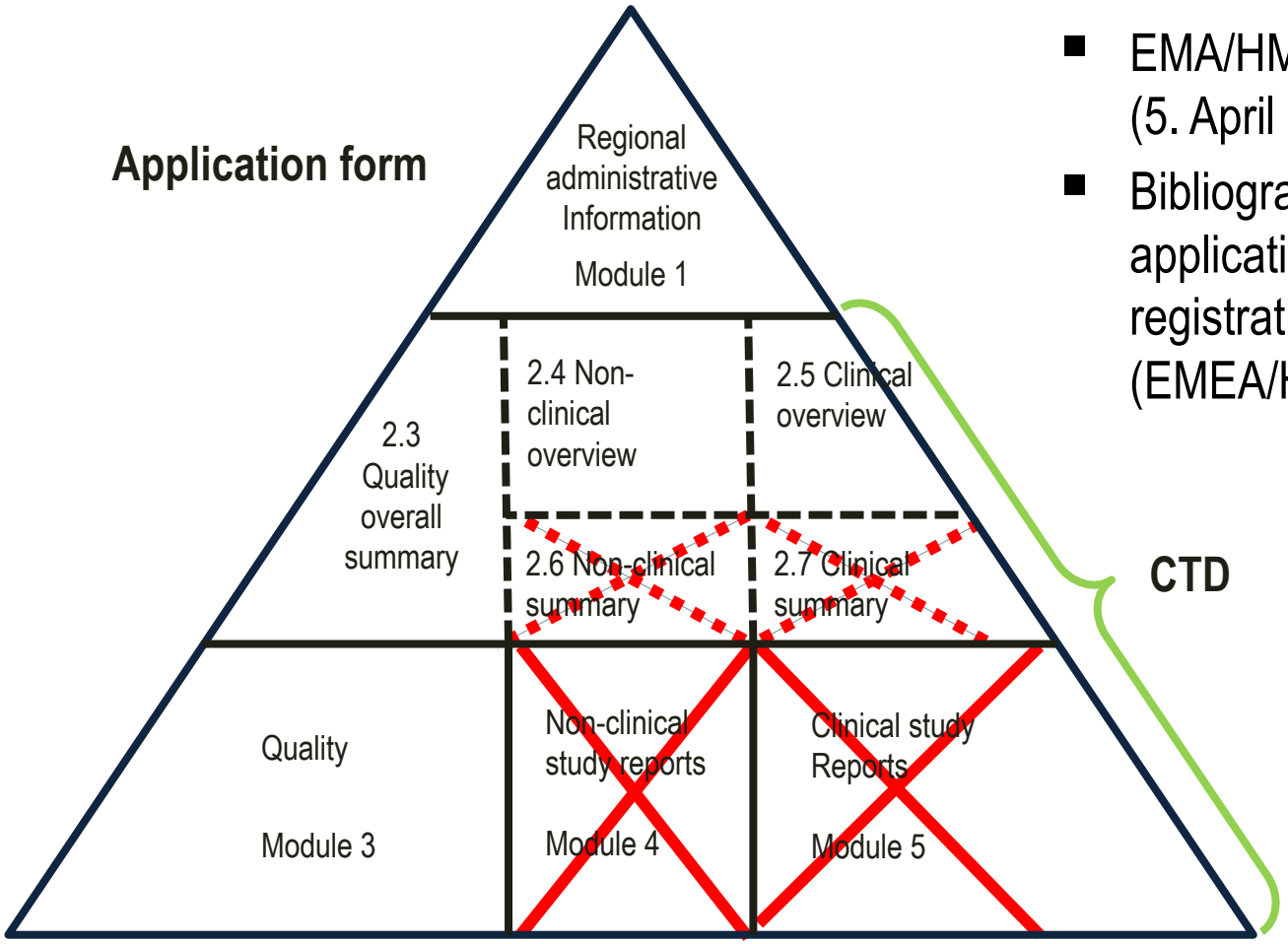
  ⇒No reduction regarding the production quality

  ⇒No reduction regarding quality documentation

  ⇒GMP for all productions steps (raw material GACP)

- Complete CTD Module 3
  - Drug substance (CTD Module 3.S.)
    - Herbal substance (herbal raw material)
    - Herbal preparation (extract)
  - Drug product (capsules, tablets, etc.; CTD Module 3.P.)
  - Including stability data (marker, reference standard, validation …)

The CTD for THMP



- EMA/HMPC/71049/2007 Rev. 2 (5. April 2016)
- Bibliographical, simplified application simplified registration (EMEA/HMPC/32116/2005)

“new” THMP?

Novelties are restricted to

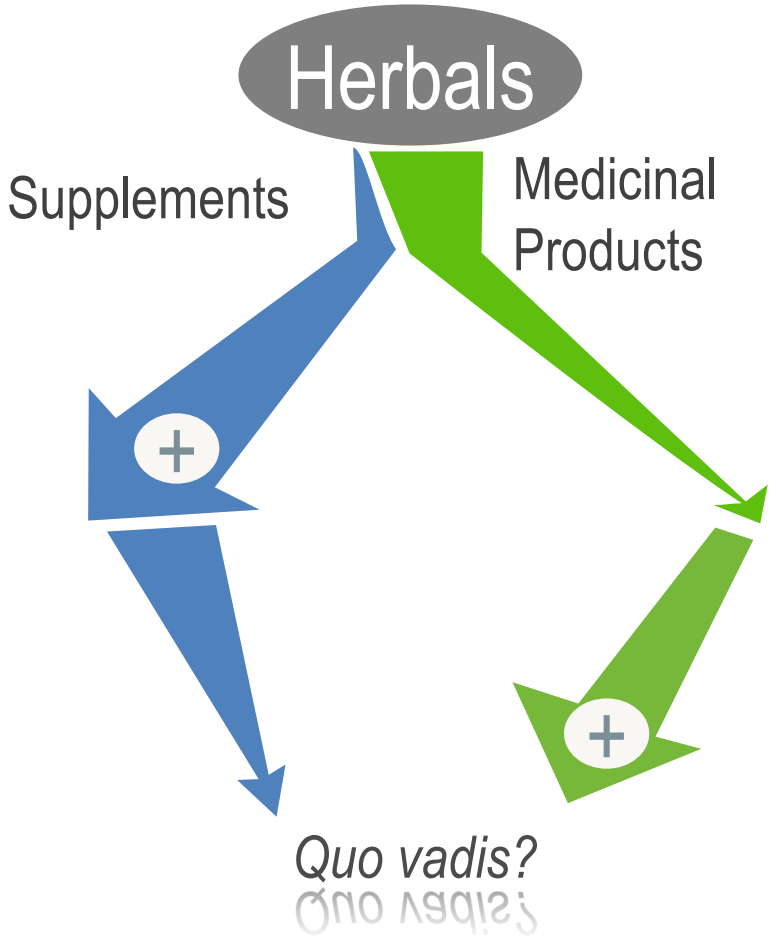
- Re-discovery of old recipes/products
- Products form eastern EU-countries
- TCM products with 15 year supplement history in EU
- Supplements with 15 y EU- (30 y world wide-) use

Future of Botanicals

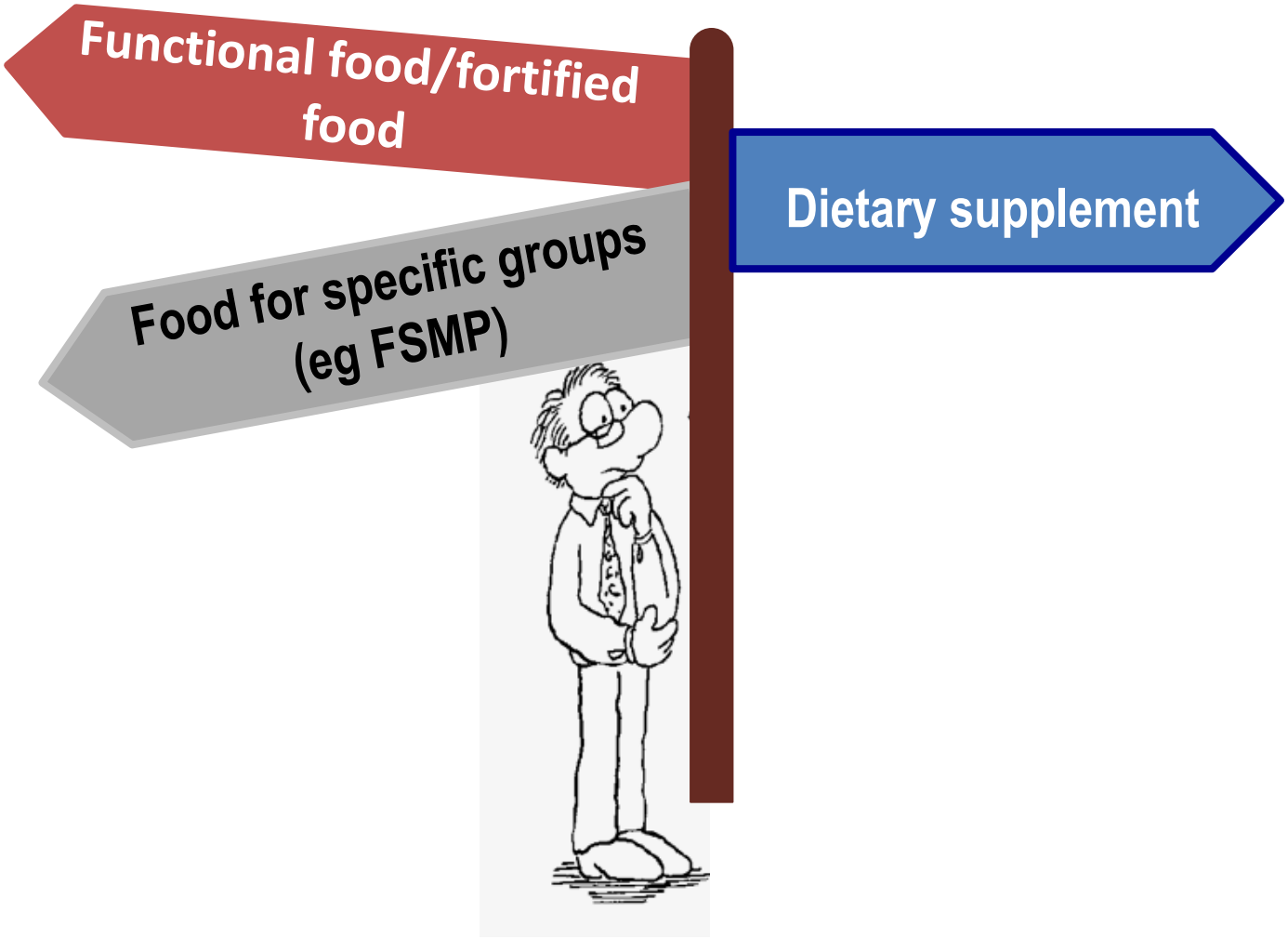
2004
EU THMP directive

2007:
EFSA NHCR came into force

2017



Food categories



Dietary Supplement: Definition

Dietary supplements are

- **FOOD (**All ingredients must be food ingredient)
- Concentrated sources of nutrients and other substances with **nutritional and physiological effect (**Uptake amount cannot exceed that which can reasonably be achieved through food use, otherwise Novel food issues may arise)
- Marketed in dosage forms: capsules, pills, sachets of powder, liquid forms
- Regulated by **European Directive 2002/46/EC**
  - Positive list of vitamin or minerals (harmonized, but not amount)
  - „other substances“ eg. herbal extracts (not harmonized)
- Health claim regulation (EC) 1924/2006 applies
- Regulation (EC) No 764/2008 on mutual recognition
  - if a product is legally on the market in one Member States then it should be allowed on the market in another (not harmonized)
- Regulation (EC) No 1169/2011 on food information to consumers

Plant Lists of EU Countries

- No harmonization of accepted herbal ingredients in EU countries
- Positive lists of plants that can be used in dietary supplements:
  - Individual lists for
    - Denmark
    - Romania
    - Germany (not legally binding)
  - BELFRIT list: Belgium, France and Italy
- EU Novel Food Catalogue (not legally binding)

Dietary Supplement: Prerequisites

What are the prerequisites for marketing of a dietary supplement

- Intended for the general and healthy population
- Specific labelling requirements
- Notification at the National Food Authorities
- Only approved nutrition and health claims are allowed
- Medical claims are not allowed
- A long term approach could be a product specific study and a health claim application

*Image courtesy of Kittikun Atsawintarangkul at FreeDigitalPhotos.net

Nutrition/Health Claims – EC 1924/2006

What's in	What it does		
Nutrition Claims	**Health Claims**		
Particular beneficial nutritional properties due to caloric value, nutrients or other substances („low fat", source of", „high in" ...) (29) Register	Functional Well-established Generic list claims	Functional Innovative	Reduction of Risk-Factor for a disease & claims on children's health and development Approval Article 14.1 (a/b)
	Relationship between a food or one of its constituents and health (body's functions)		
	Register (2012) Article 13.1	Approval Article 13.5	

Health Claims Accepted by EU Commission

http://ec.europa.eu/food/safety/labelling_nutrition/claims/register/public/?event=search

Acceptance Rate of Health Claims

Claim type	Authorized	Non-authorized	Total	Acceptance rate
Article 13.1	229	1875	2104	10.9%
Article 13.5	10	108	118	8.4%
Article 14.1a (risk reduction)	14	24	38	36.8%
Article 14.1b (children)	12	44	56	21.4%

Data based on EU Register of Nutrition and Health Claims, February, 2017

How to get a Health Claim?

- Most supplements are only attractive with a health claim

Approved ingredient dependent health claim (13.1)	⟷	Product specific health claim (13.5/14.1)

  - Find a suitable ingredient with a suitable claim from the generic 13.1 list
  - add your ingredient

⇒ new combination with claims

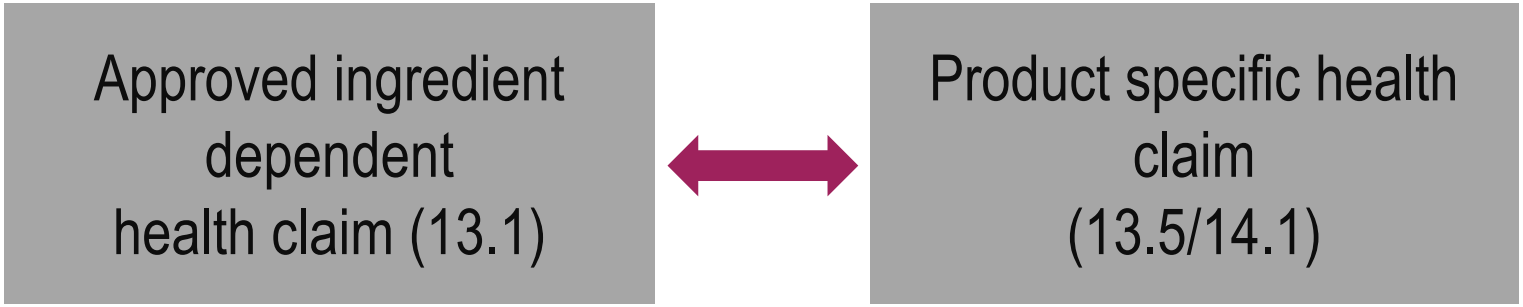
Health Claims: Positive List (13.1.claims)

Compound	13.1. Claim	Conditions of use
Copper, Zinc, Folate, Iron, Selenium, Vitamin A, B12, B6, C, D	[NAME OF VITAMIN/S] AND/OR [NAME OF MINERAL/S] contributes to the normal function of the immune system	for food, which is at least a source of [NAME OF VITAMIN/S] AND/OR [NAME OF MINERAL/S] referred to in the claim (15% of the NRV)
Vitamin C	Vitamin C contributes to maintain the normal function of the immune system during and after	
Activated charcoal	Activated charcoal contributes to reducing excessive flatulence after eating	before and 1 g shortly after the meal
Beta-glucans	contributes to the maintenance of normal blood cholesterol levels	with a daily intake of 3 g of beta-glucans from oats, …

Differentiation from other products is difficult

How to get a Health Claim?

- Most supplements are only attractive with a health claim



- Product specific study
- Product specific health claim application

Product Specific Claims (Art. 13.5/14)

- **Requirements* for individual application**
  - Characterization of the food/constituent
  - Demonstration of the claimed effect
  - Relevance for human health by convincing clinical data (placebo-controlled, double-blind gold standard trials)
  - Plausible mode of action
  - Bio-availability
  - Dose-response relationships (if applicable)
- **Submission to any national food agency; evaluation by EFSA**
- **No associated fees**
- **Data designated as proprietary are protected for 5 years**
  - → Applicants get their **own protected claim,** which cannot be used by competitors

*According to NDA panel members

Health Claim Substantiation

Looking through EFSA glasses

Assessment by EFSA

First basic questions

- Is the food/constituent sufficiently defined/characterized?
- Is the claimed effect beneficial to human health?
- Is the cause-and-effect relationship established?

fail one = fail all

Second set of questions

- Is the quantity of food/consumption pattern adequate?
- Does the claim wording reflect the scientific evidence?
- Does the claim wording comply with the regulation?
- Are the conditions of use appropriate?

EFSA requirements - Food characterization

- Characterization incl. source, specification (physical and chemical properties)
- Manufacturing process (ISO, GMP, HACCP etc.)
- Stability data such as storage conditions and shelf-life
- Batch-to-batch variability data
- Data on bioavailability
  - Rationale
  - Scientific data for the use of the constituent by the human body
  - Reaching target site
  - Factors that may affect absorption

EFSA requirements – Beneficial claimed effect

- **Is the claimed effect beneficial to human health?**
  - The food/ingredients have to have a beneficial nutritional or physiological effect
  - It has to be clearly defined and beneficial to the target population
  - Claimed effects need to be specific enough to be testable and measurable by generally accepted methods *in vivo* in humans
    - Not suited for the general population (according EFSA NDA Panel):
      - "a reduction of gastric acid levels" or "a reduction of inflammation"
    - Possible claims are:
      - Reduction of excessive intestinal gas accumulation

EFSA requirements – Cause-&-effect-relationship

Is the cause-and-effect relationship established?

- This has to be shown by human clinical data
- The “cause-effect” has to be shown by statistically significant differences between the group treated with the substance (=cause) and the control group in randomized controlled clinical trials
- *In vitro* and *in vivo* data is important as supporting evidence (biological plausibility)

EFSA requirements – Study population

Healthy people: Small effect size	people at risk	Diseased patients: Large effect size
Not appropriate as they are too healthy!	**No longer healthy but still not sick?**	**Not appropriate; only as supportive evidence**
*  *Image courtesy of Vladoat FreeDigitalPhotos.net;	**e.g. IBS patients for gastrointestinal discomfort**	

Human study-related reasons for rejection

- Food constituent used is not identical with the product
- Different dosing regime
- Study population does not represent general population
- Primary endpoint is not suitable/accepted to prove the claimed effect
- Missing evidence for a mechanism (*in vivo* in human)
- Methodological limitations related to treatment allocation, randomization, blinding
- Risk of bias
- No statistical significance/study underpowered

Timelines

Study preparation 3-4 months

- Preparing and finalizing study documents (study plan, CRF, study participant information, statement of consent)
- Filing and defending documents with the ethics commission
- Study preparations (adequate placebo, random list etc.) from sponsor

Clinical part 4-x months

- Subject inclusions (number, indication)
- Duration of intervention (indication, EFSA guidance)

Data management 2-4 months

- Data entry, data cleaning
- Blind data review
- Statistical analysis
- Final report

HC application

- Drawing up of Health Claim application (2-3 months)
- Submission to the national authority (1-x months)
- EFSA completeness check (1-2 months)
- Scientific evaluation incl. Clock Stop (5-8 months)

1 – 2 years

1 – 2 years

Natural Health Products as Medical Device?

According the New Medical Device Regulation (10728/4/16 REV 4 51) "A 'medical device' means:

… **any** instrument, apparatus, appliance, software, implant, **reagent, material** or other article intended by the manufacturer **to be used**, alone or in combination, for human beings for one or more of the following **specific medical purposes**:

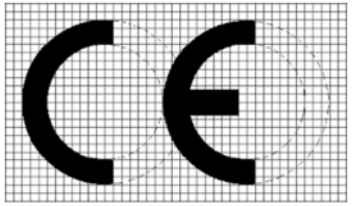
- diagnosis, **prevention,** monitoring, prediction, prognosis**, treatment** or alleviation of disease,
- … ,
- … ,
- … ,

and which **does not achieve** its principal intended action **by pharmacological, immunological or metabolic means,** in or on the human body, but which may be assisted in its function by such means.

Natural Health Products as Medical Device?

- Natural ingredients can either
  - act by **physical means** (eg. absorbents due to fibers, microorganisms)
  - may **assist the medical function by pharmacological, immunological or metabolic** means (eg. melissa in patches)
  - might be included as **flavoring agents** (eg. ginger)

$\Rightarrow$ Substance based, even oral medical devices are possible, as long as the principal mode of action is **physical**



Medical device: scientific data

Basic requirement of non-clinical and clinical data

- Biological evaluation
  - Biocompatibility tests according ISO 10993 / Bibliographic data
- Clinical evaluation
  - Clinical trials in accordance to ISO 14155 / Bibliographic data
- Manufacturing according to QMS ISO 13485
- Establishment of a RMS according to ISO 14971
- Stability data
- Technical documentation (TD)
- Medical device with pharmacological actives (class III) have to undergo a consultation procedure (national drug authority will be involved)

⇨ **Finally get your CE mark on your product**

Examples:
Substance-based Medical Devices

Examples of substance based MD (under the old Medical Device Directive)

- Fibers, with fat absorbent capacity for slimming
- Lozenges with sage, myrrh, Iceland moss for sore throat
- Nose spray, creating a barrier for allergy
- Wound care dressing with natural oils
- Medihoney for wound care

Summary: Comparison of product categories

	Supplement	THMP	Medical Device
Ingredients	Food	Herbals/ minerals/ vitamins	All kind of actives
Main regulation	Directive 2002/46/EC Regulation EC 1924/2006	EU Directive 2004/24/EC; *Article 16a* of Directive 2001/83/EC	Old:MDD 93/42/EEC New:MDR
Action	Physiological	Pharmacological	Mainly physical
Market entry	Notification	Registration based on tradition	Authorization based on bibliographic and clinical data (vcertificatio process with notified bodies)
Claims	Nutritin / health claims	Soft medicinal claim: „Traditionally used …"	"for supportive treatment of [disease]"
Claim Substanciation	• at least 1 – 2 RCT • mode of action study • EFSA approval	• Proof of tradition • Ames test • National simplified drug registration	Depending on classification: • Class IIa: at least 1 RCT • Biocompatibility test • QMS / RMS • Technical documentation
Target group	Healthy consumer	Self-medication	Self-medication
Advantage	Fast market access	Higher retail price	Higher retail price Access to total EU
Disadvantage	Proprietary claims are time and cost intensiive	Copy cats	Restricted to certain products

Summary: Time and Investment

Approach	Time to market	Investment
Old formulation new packaging of THMP	+	+ (+)
Non EU traditional products as THMP	+++	++
Food Supplement w/o proprietary claim	+	+
Food Supplement with proprietary claim	+++	+++
Medical device	+	++
New Ingredients as Novel Foods	+++	++

a&r overview

More than 20 years: “Your innovation experts in natural health products”

35 professionals passionate for your natural health products

Food | Nutraceuticals | Herbal drugs | Medical devices | OTC

Consulting & Strategic Innovation

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Regulatory Creativity

a&r
Scientific Marketing

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Innovation

Clinical Research (CRO)

a&r
Clinical science

a&r
Study Design

a&r
Study Center

Thank you for your attention !

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