PYME INNOVADORA

GOBIERNO DE ESPAÑA
MINISTERIO DE ECONOMÍA, INDUSTRIA Y COMPETITIVIDAD

NUTRACEUTICALS
New Trends

Gemma Casadevall, PhD.

NUTRA RESEARCH

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OUTLINE

01 Basic Aspects

02 Dosage Forms

03 Regulatory Aspects

04 Ingredients

05 Formulation Technologies

06 Quality Aspects

06 Innovation

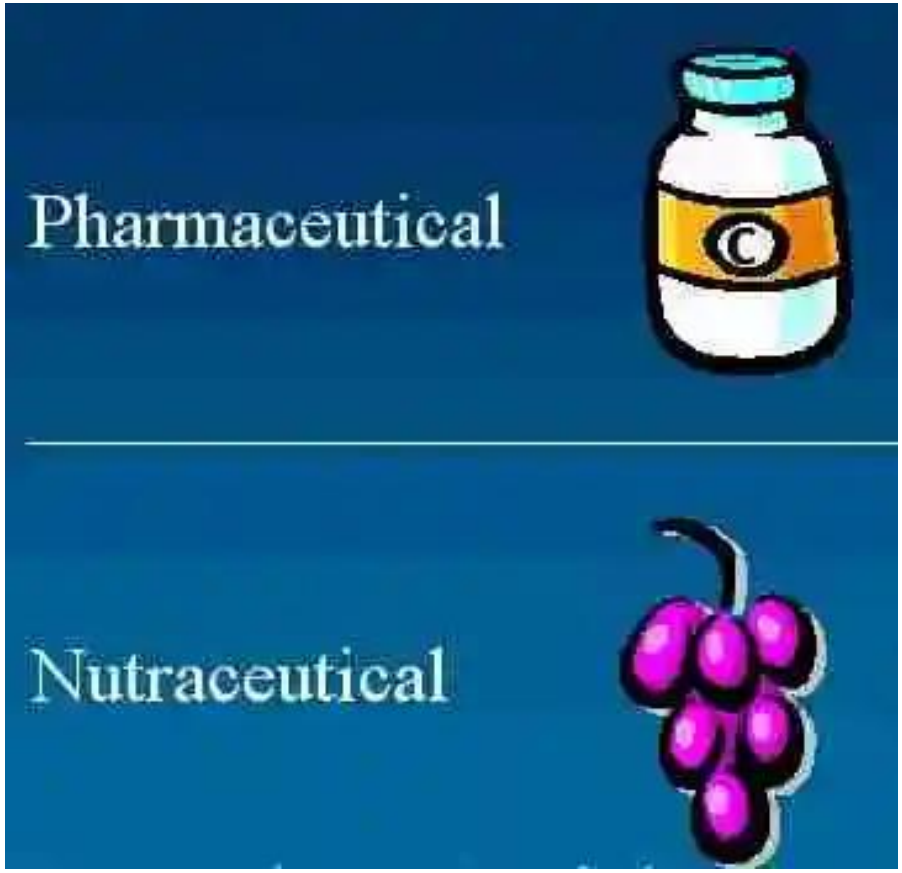
BASIC ASPECTS

What are nutraceuticals?

- Nutraceuticals are products made from natural sources that have health benefits beyond the basic nutritional value found in food.
- Nutraceuticals are used to promote general well-being and prevent illnesses. They are meant for healthy people.
- There is no globally-accepted definition for what a nutraceutical is, so definitions, attitudes and legislation around nutraceuticals are different from country to country.

- Thus, Companies must design and place on the market robust products, from the legal, efficacy, safety and quality point of view FROM THE DESIGN allowing then to choose target markets under the best possible conditions

In summary…



TREAT AND PREVENT
A DISEASE

KEEP YOU HEALTY

Types of nutraceuticals

Nutraceuticals fall into two general categories:

- **Food/Nutritional supplements:** In addition to vitamins, dietary supplements can contain minerals, herbs, amino acids, enzymes and many other ingredients.

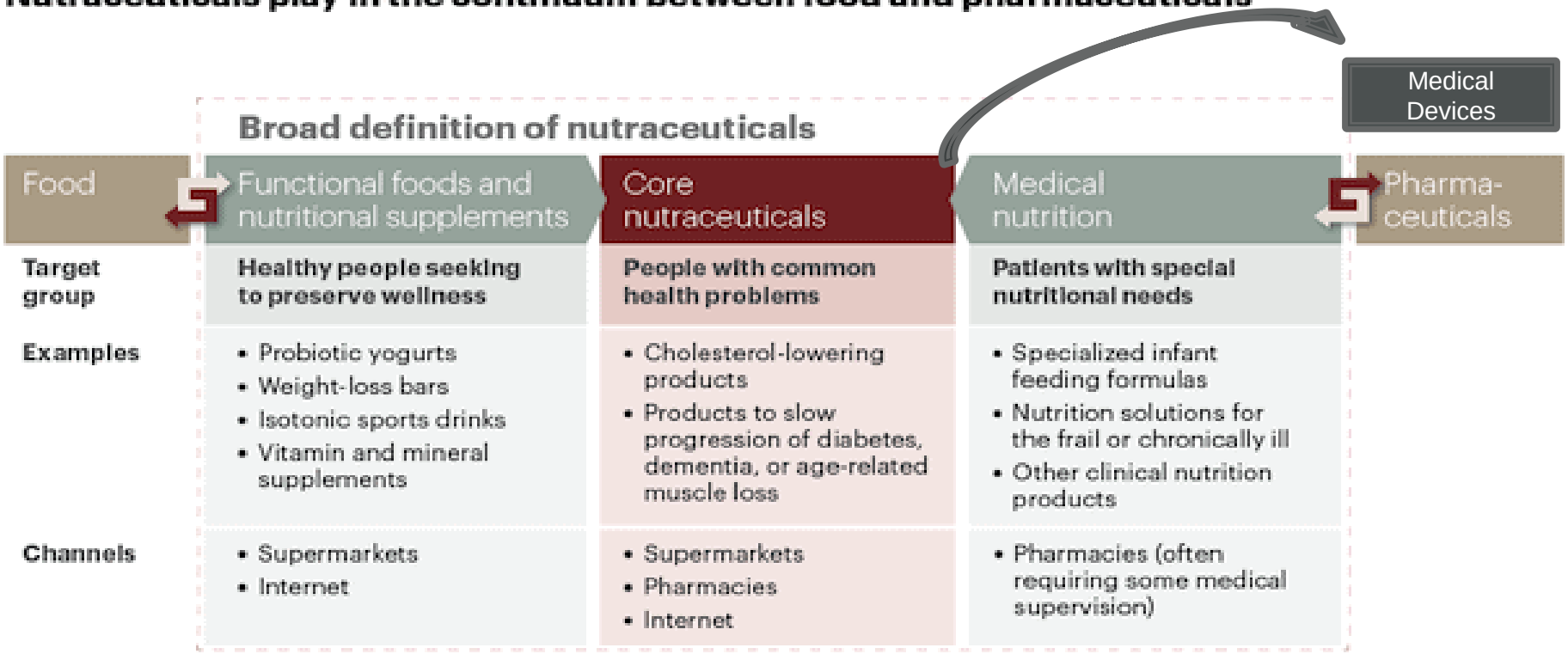
- **Functional foods:** This includes whole foods and fortified, enriched or enhanced dietary components.

  - Conventional functional foods are nutrient-rich foods (legumes and whole grain products).

  - Modified functional foods: include juices with added calcium, cereal with added iron, or milk with added zinc and folic acid

Nutraceuticals Arena

Nutraceuticals play in the continuum between food and pharmaceuticals



Source: A.T. Kearney analysis

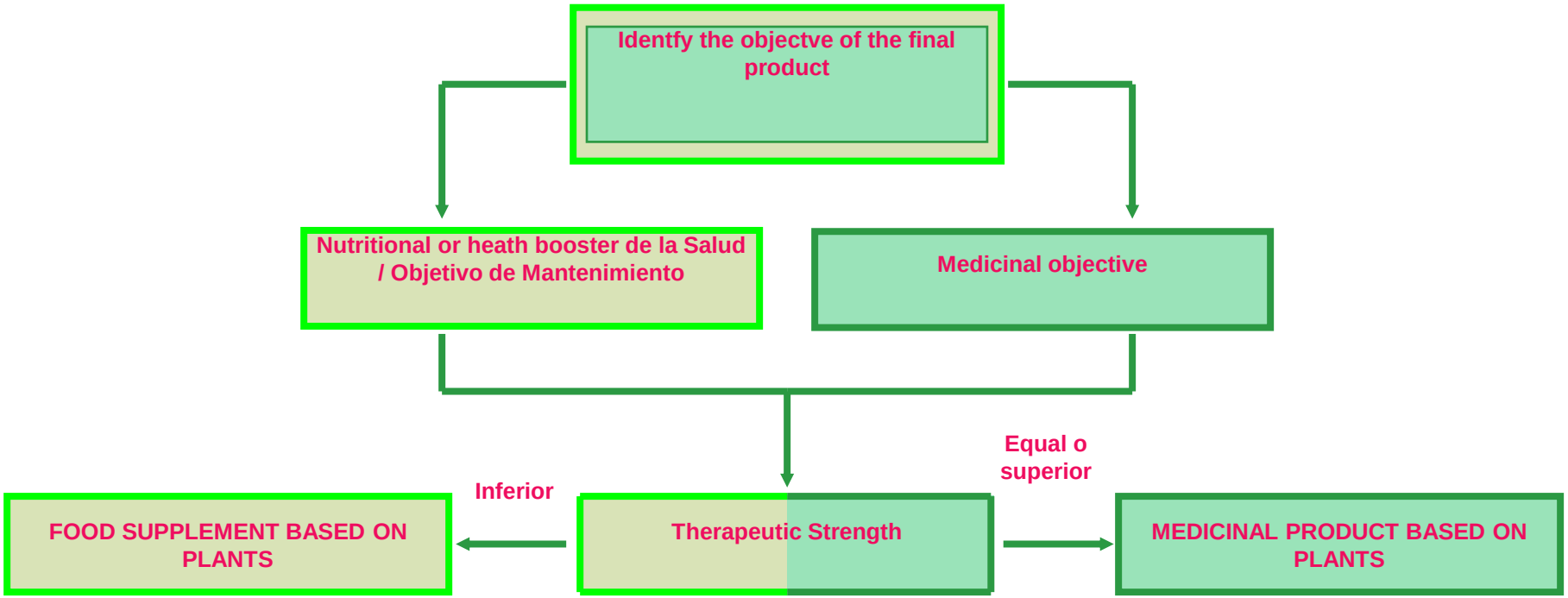
Not only many consumers want to take an active role in preventing illnesses, but now new trends ask for "more natural alternatives".

This is where nutraceuticals come into play — midway between the consumer market and the scientific world of pharmaceutical firms.

Under Regulatory Perspective:

Therapeutic vs. Phisiological effect

Use of plant based ingredients:

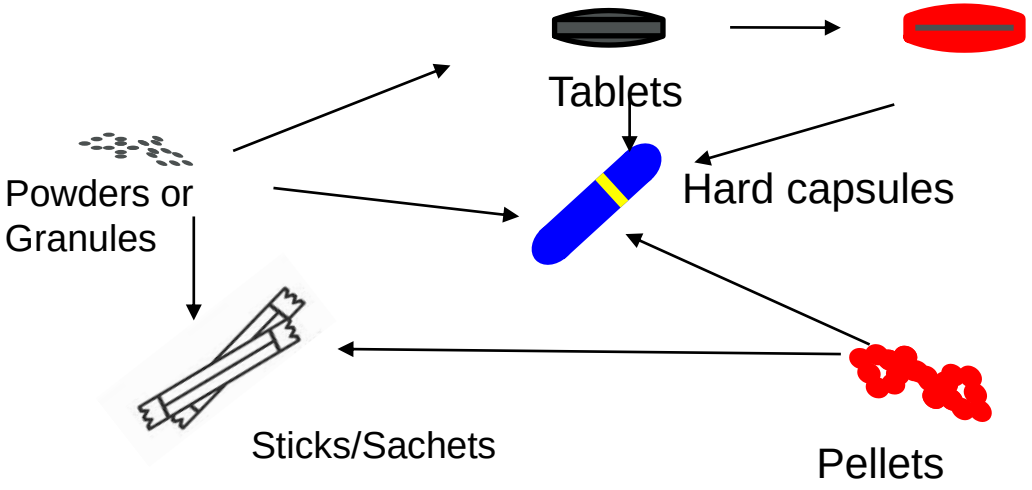


DOSAGE FORMS

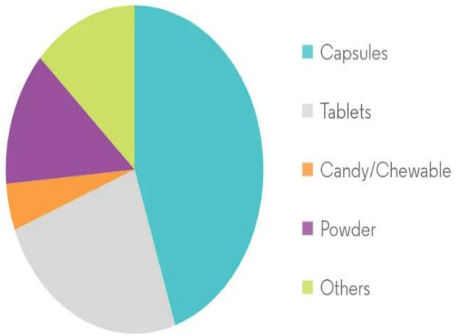
Is this really different than pharma?

Market data

"Food supplements … may be dosed in formats such: capsules, tablets, or other similar forms, powder sachets, liquid ampoules, dropper bottles and other similar forms, of liquids and powders to be taken in small unit amounts"

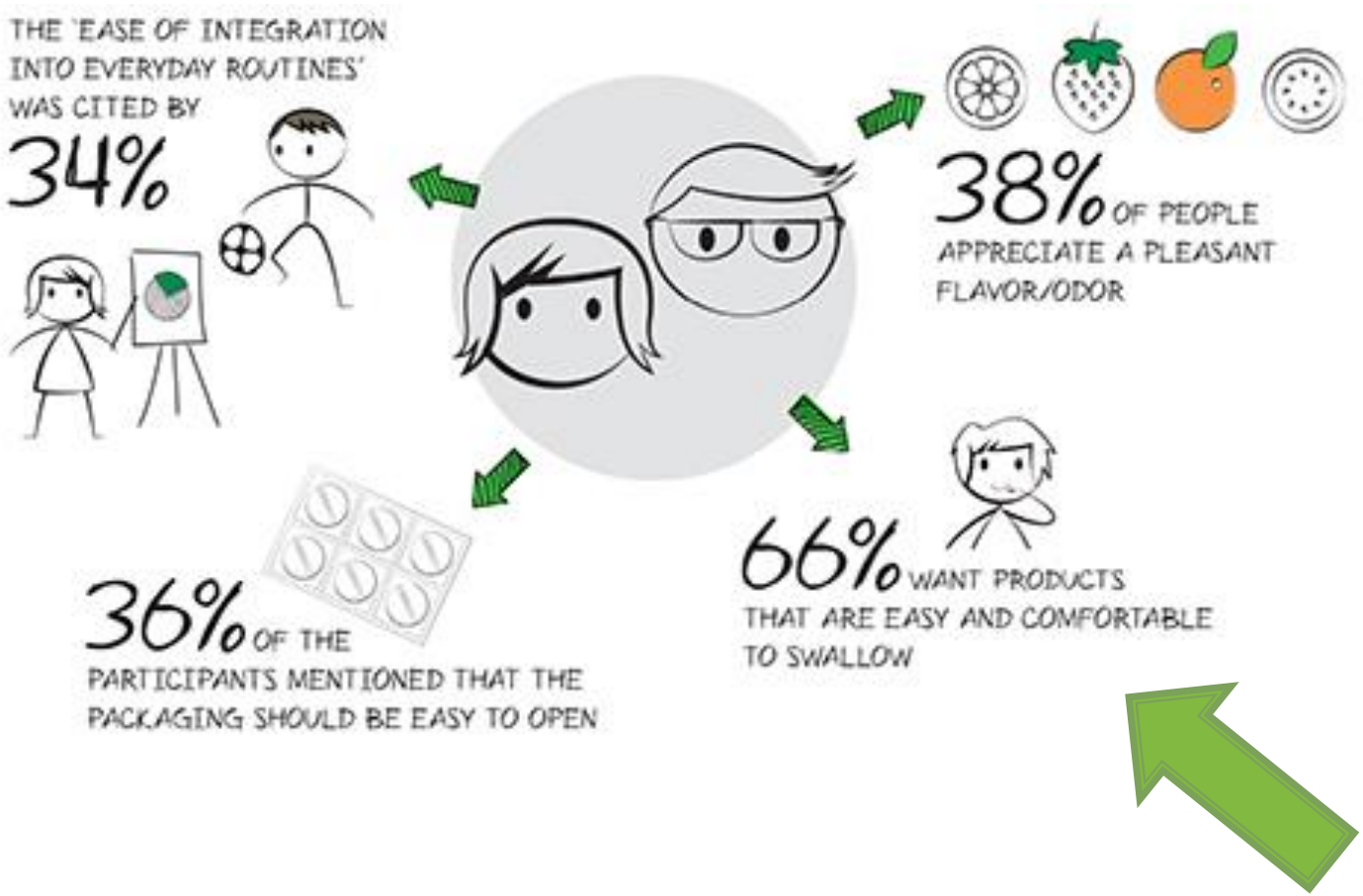


New Product Launches, % Share, by Product Form, Dietary Supplements, Global, 2019



Source : Mordor Intelligence

What really matters....



EU Regulatory Requirements

Materials in contact with food

Regulation (EC) 1935/2004.

Manufactured according to food GMPs of Regulation (CE) 2023/2006.

They should not transfer their components to food in contact that may:

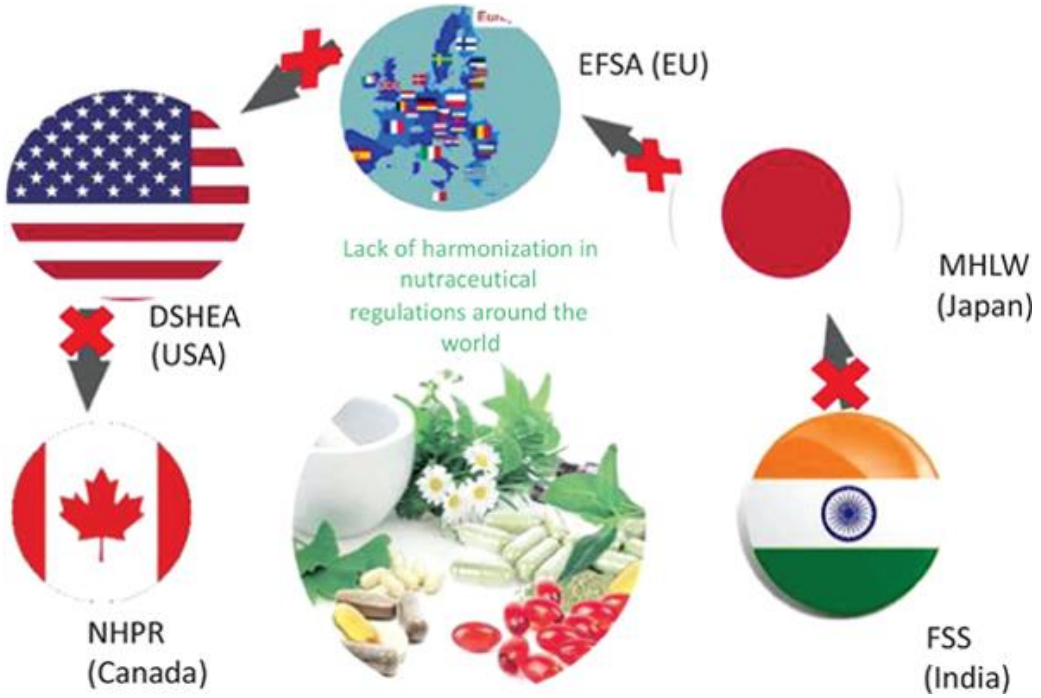
- Represent a danger to human health.
- Cause an unacceptable change in the composition of food.
- Cause an alteration to the organoleptic characteristics.

REGULATORY ASPECTS

Food Supplement Regulations

Regulations placed on nutraceuticals vary widely around the world. Thus, industry regulations often fall into a grey area where information and expectations can be unclear.

Both manufacturers and consumers should be aware of their country's nutraceutical regulations to make safe and informed final products.



Regulations EU I

- The European **Food Safety Authority (EFSA)** defines and regulates nutraceuticals as **food supplements**, a concentrated dose of nutrients to accompany normal dietary intake and provide nutritional and/or physiological benefits.

- The main focus is placed upon the ingredients - including vitamins, minerals, and amino acids - and the levels at which they are present in the supplement. Nutraceuticals produced in the EU must **only** contain substances approved and published in the Directive 2002/46/EC.5

- Any company wishing to include a vitamin, mineral, or other substance that is not included on this list can submit an application to the EC for consideration.

- Regarding Nutrition and **Health Claims**, the European Commission has established Union rules through Regulation (EC) No 1924/2006. The Regulation started to apply on 1 July 2007.

Regulations EU II

- This regulation is the legal framework used by food business operators when they want to highlight the particular **claim** effects of their products, in relation to health and nutrition, on the product label or in its advertising.

- The rules of the Regulation apply to nutrition claims (such as "low fat", "high fibre") and to health claims (such as "Vitamin D is needed for the normal growth and development of bone in children").

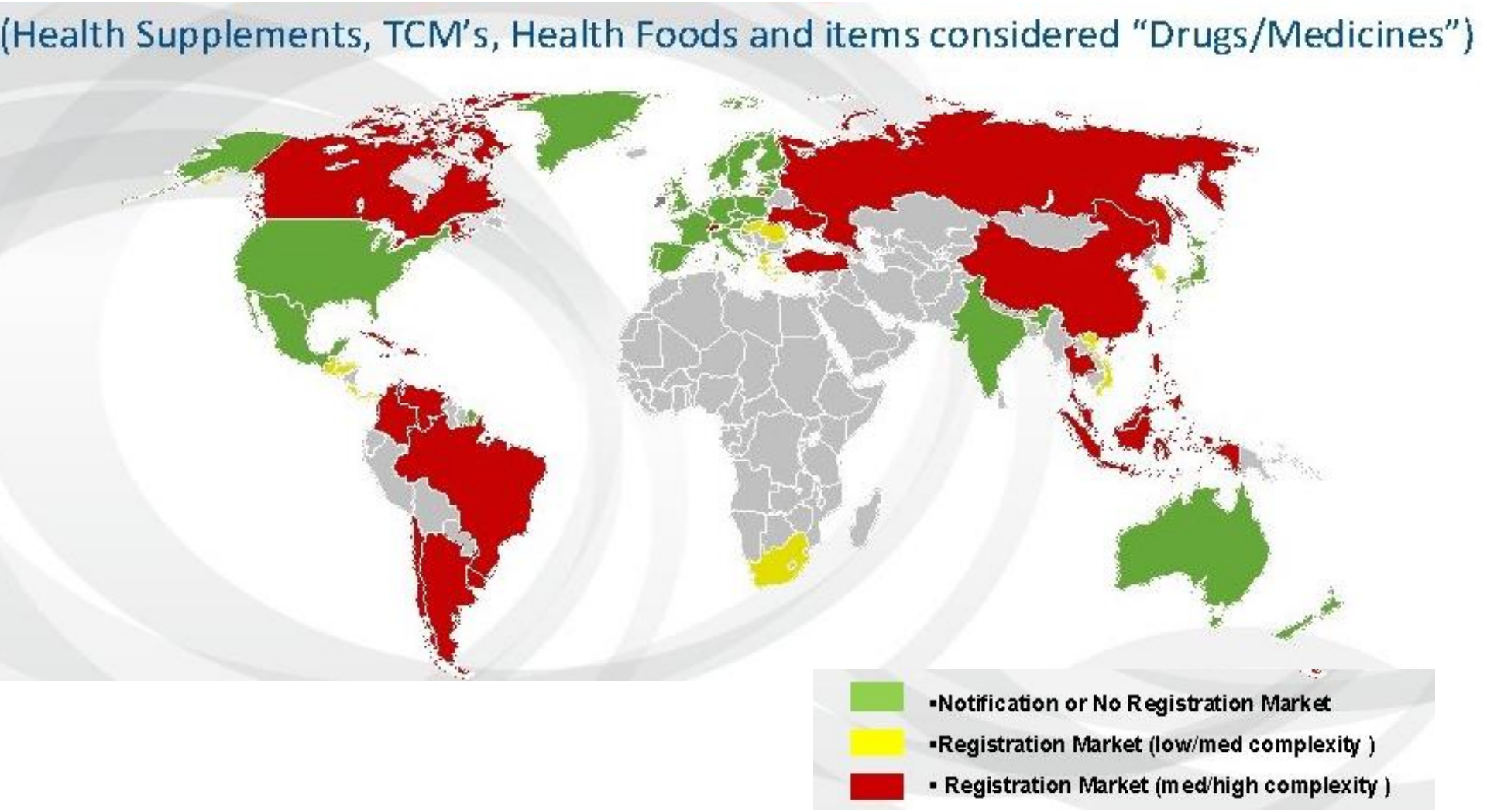
- The objective of those rules is to ensure that any claim made on a food's labelling, presentation or advertising in the European Union is clear, accurate and based on scientific evidence.

- This not only protects consumers, but also promotes innovation and ensures fair competition. The rules ensure the free circulation of foods bearing claims, as **any food company may use the same claims on its products anywhere in the European Union**.

- Under the fifth transitory provision of ART 27.5 of regulation 1924/2006 "on hold or pending" can be used.

Regulations WW map

(Health Supplements, TCM's, Health Foods and items considered "Drugs/Medicines")



Allowance of Ingredients

Market	Allowed "Existing" Ingredients	"New" Ingredients
EU	• Used before 1997 (FS Directive) • Vitamin & Mineral positive list • Other Ingredients regulated at Member States level – some Positive	• Novel Ingredient authorization
USA	• Used before 1994 (DSHEA)	• New Dietary Ingredient (NDI) notification (exempt from notification if in food supply)
ASEAN	• Negative list • Restricted condition of use list	• Self assessment of safety and not meet criteria for inclusion in Negative list
Japan	• Positive list for use in foods • List of not drug ingredient • Part of food supply	• Self or Government assessment if food or drug ingredient
Korea	• Health Functional Food (HFF) Code • Part of food supply	• New HFF Ingredient authorization
China	• Positive list for use in foods & drugs • Positive list for use in health foods • Negative list for use in health foods • Part of food supply	• no specified regulation/process

INGREDIENTS & RAW MATERIALS

-Actives
-Excipients

ACTIVES

VITAMINS
MINERALS

Based on Reglamento CE1170/2009, lists of vitamins and minerals

VEGETAL SPECIES: PLANTS OR EXTRACTS

OTHER INGREDIENTS: Essential fatty acids (EPA / DHA)

-Probiotics, Prebiotics, Postbiotics
-Actives (Routine, Melatonin).
-Amino acids (Tryptophan)
-Phytosterols
-Enzymes
-Clays

EXCIPIENTS

In *Spain* according to Reglamento 1129/2011 additives

ACTIVES

EFFICACY

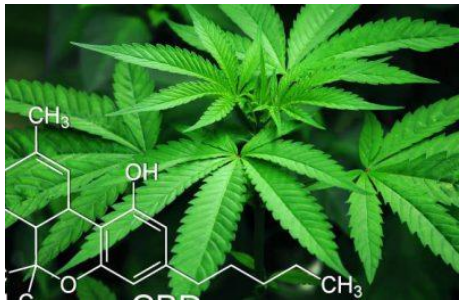
- Physiological (pharmacological) action
- Choose the raw materials that have a proven physio-pharmacological action for the condition we are looking for, according to the scientific literature available at the time

SAFETY & TOXICITY

- Formulations must be Safe
- Rule out toxic substances or substances with significant side effects.
- Choose safe raw materials with extensive experience of use.
- Choose EFSA approved substances

ACTIVES

NOVEL FOODS I



Novel Food is defined as food that had not been consumed to a significant degree by humans in the EU before 15 May 1997, when the first Regulation on novel food came into force.

Can be newly developed, innovative food, food produced using new technologies and production processes, as well as food which is or has been traditionally eaten outside of the EU. Therefore, there are positive and negative lists.

Examples: new sources of vitamins or extracts from existing foods, agricultural products from third countries or food derived from new production processes, now, CBD

ACTIVES

NOVEL FOODS

"Cannabis" – Cannabinoids - Cannabidiol

efsa
European Food Safety Authority

Novel Food Catalogue

- Cultivation of *Cannabis sativa* L. is permitted provided they are registered in the EU's 'Common Catalogue of Varieties of Agricultural Plant Species' and THC content does not exceed 0.2 % (w/w)
- Extracts of *Cannabis sativa* L. and derived products containing cannabinoids are considered novel foods
- Synthetically obtained cannabinoids are considered as novel

3 CBD under EFSA RISK ASSESSMENT

ACTIVES

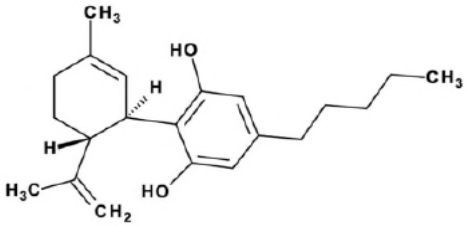
NOVEL FOODS

Cannabidiol

efsa
European Food Safety Authority

- EMA has recently approved Epidyolex which active substance is CBD from the milled botanical raw material (Cannabis sativa L.). Epydiolex is an adjunctive therapy for seizures associated with Lennox Gastaut syndrome (LGS) or Dravet syndrome (intractable childhood epilepsy) for patients 2 years of age and older.

- EFSA assessment will perform an **independent RA**:
  - Assessment is NOT based on risk-benefit
  - EFSA target general population, not patients
  - Different production process

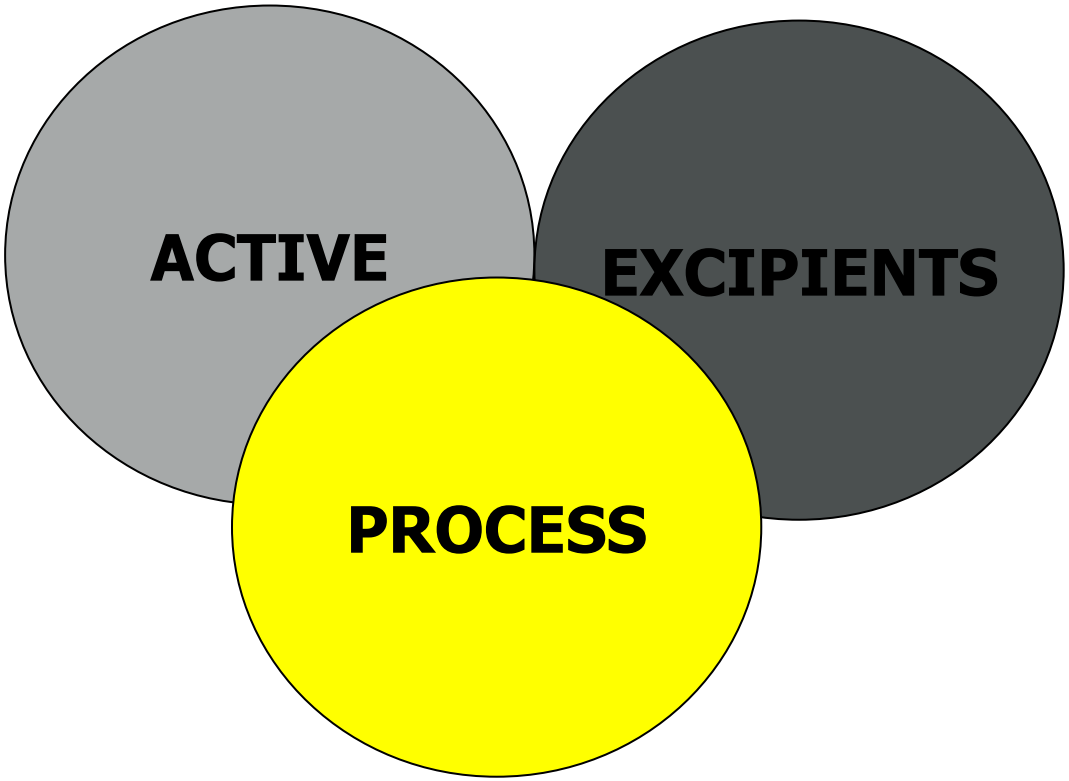


- Evaluation of CBD will follow the approach from EFSA NDA Guidance for NF

EXCIPIENTS

ACTIVES+ EXCIPIENTS + PROCESS=

NUTRACEUTICAL



Is this really different than pharma?

EXCIPIENTS

Table II: Key differences between food ingredient good manufacturing practices (GMPs) and excipient GMPs.

Food ingredient GMPs	Excipient GMPs
Primary focus: Identify and control hazards.	Primary focus: Verify process controls are sufficient to reproducibly produce excipients of consistent quality.
Written food safety plan available at all food facilities, which includes the preventive controls for identified food safety hazards.	Assessment of risks is required; however, a single documented risk assessment plan is not required.
Identity of preventive controls qualified individual (PCQI) responsible for: • Preparation of the food safety plan • Validation of the preventive controls • Reanalysis of the food safety plan	No equivalent requirement.
Activities can be managed by shared responsibility. Quality unit is responsible for oversight, but responsibility can be delegated.	Quality unit independent of manufacturing is responsible for: • Approval of documents that impact product quality • Approval of significant changes* that may impact excipient quality • Approval of suppliers • Release of finished excipient • Approval to reprocess and/or rework • Approval of returned excipient for resale • Review and approval of manufacturing, packaging, labeling, and testing records prior to approval.
Minimum personnel gowning/hygiene defined in regulation.	Personnel gowning/hygiene determined by risk assessment.
Allergen control plan required.	Allergen control is customer driven but not required by GMP.
Documented recall plan, which must include conditions and process for informing the public.	Documented recall procedure; public notification is not required.

SUPPLIER QUALIFICATION

- RSI (Industrial Sanitary Registry)
- Mandatory for all food products
- Auditable
- API suppliers MUST BE authorized
- Manufacturers, Distributors, Warehouses must be able to provide necessary documentation:
  -Technical file
  -Allergen declaration
  -GMO free declaration
  -Safety data sheets
  -Nutritional information
  -Analytical methods

FORMULATION TECHNOLOGIES

Formulation Challenges

MUST HAVE: SAFETY; EFFICACY & STABILITY

• Quality control of crude plant drugs is more complex than for single chemical entities.

• Production methods used for plant derived medicines are necessarily more involved than for single chemical entities.

• Due to the complex nature of plant-derived materials as drugs, they present a wide range of formulation problems.

• There are a number of pharmaceutical issues related to plant medicines, including variability, quality, bioequivalence, and adverse effects.

Formulation Challenges

Botanicals are complex:

- Formulations contain always multiple actives (extracts)
- 70% of the formula can be active compounds (with high variability, due to natural sources)
- Strong sensitivity of ingredients to heat and moisture
- Must identify good specifications for identity, purity, strength, composition and Shelf life

Formulation Steps

Is this really different than pharma?

Feasibility Study

Pre Formulation Tests

Pilot trials

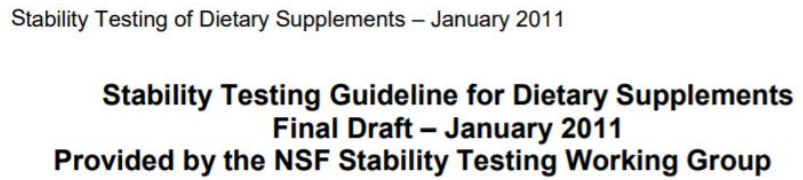
Stability Tests

Validation of the formulation & Scale up

Stability tests

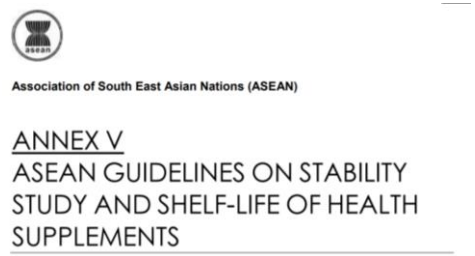
Because everything is unstable….

Most country regulations do not require stability testing as mandatory for food supplements, nevertheless most countries have started releasing guidelines as common good practice to support shelf-life.


Stability Testing of Dietary Supplements – January 2011

Stability Testing Guideline for Dietary Supplements
Final Draft – January 2011
Provided by the NSF Stability Testing Working Group

Organization	Guidelines
ASEAN	Guideline "Stability Studies of Drug products"
US-FDA	Guidance for Industry "Stability Testing of Drug Substances and Drug Products; June 1998"
WHO	TRS 863, Annex 5: "Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms"
EMEA	Note for Guidance on Stability Testing of existing active substance and Related Finished products (Draft), February 2002


Association of South East Asian Nations (ASEAN)

ANNEX V
ASEAN GUIDELINES ON STABILITY STUDY AND SHELF-LIFE OF HEALTH SUPPLEMENTS

Stability tests

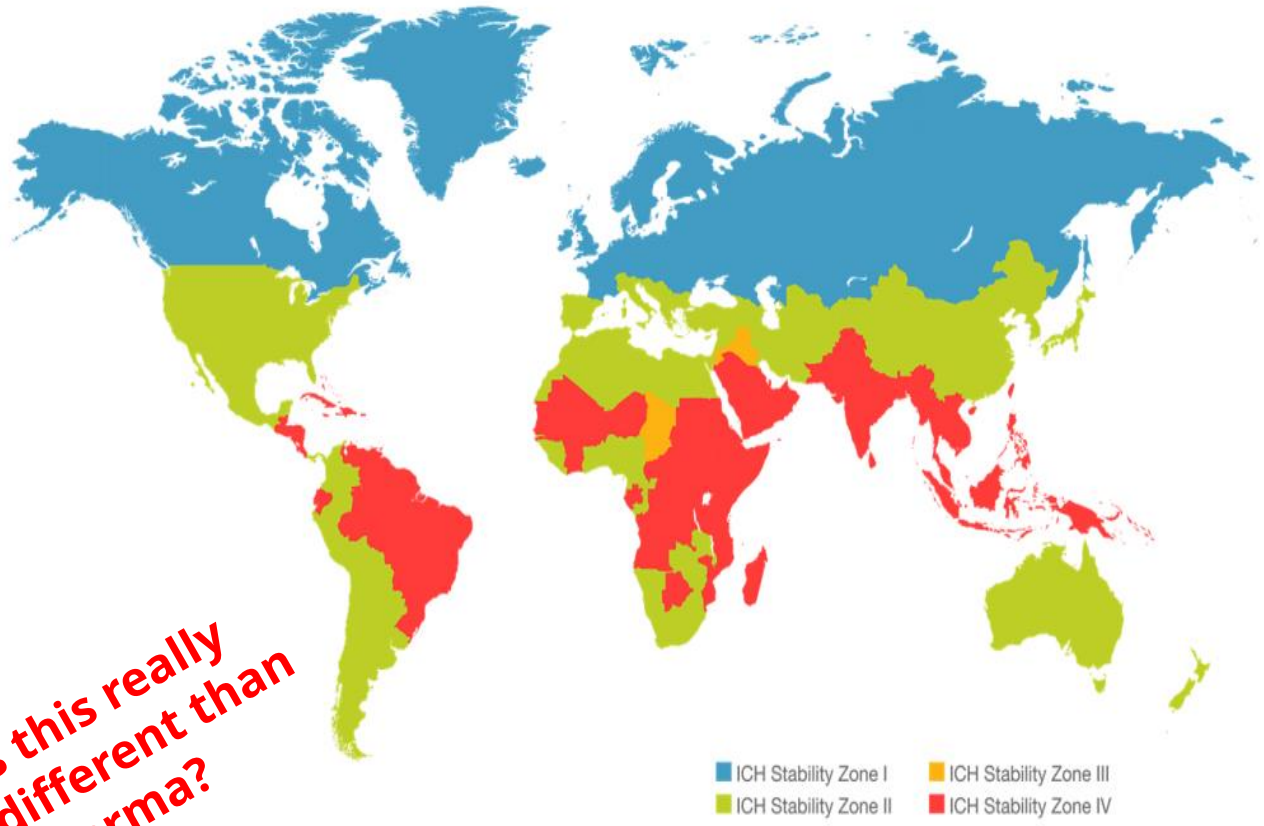
It’s recommended to follow ICH Q1A

European Medicines Agency

August 2003
CPMP/ICH/2736/99

ICH Topic Q 1 A (R2)
Stability Testing of new Drug Substances and Products

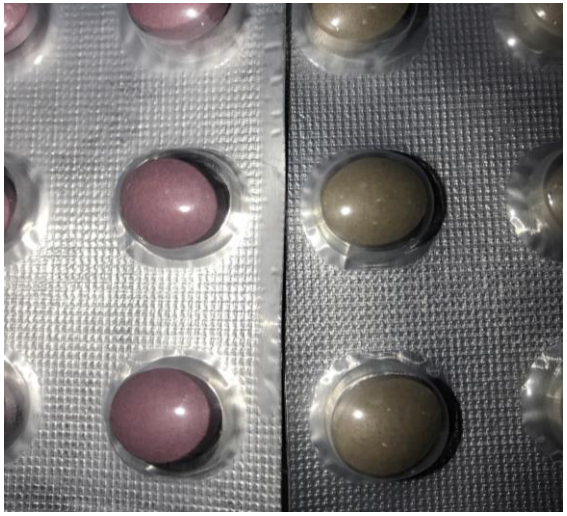
Climatic Zone	Countries
Climatic Zone I	"Temperate" — Japan, United Kingdom, Northern Europe, Canada, Russia, United States
Climatic Zone II	"Mediterranean, Subtropical" — Japan, United States, Southern Europe
Climatic Zone III	"Hot, dry" — Iran, Iraq, Sudan
Climatic Zone IV	"Hot, humid" — Brazil, Ghana, Indonesia, Nicaragua, Philippines



Is this really different than pharma?

Stability tests

Sure!, it's NOT mandatory...but there is a price to everything...



Assay: Extracts

-Valeriana raíz polvo

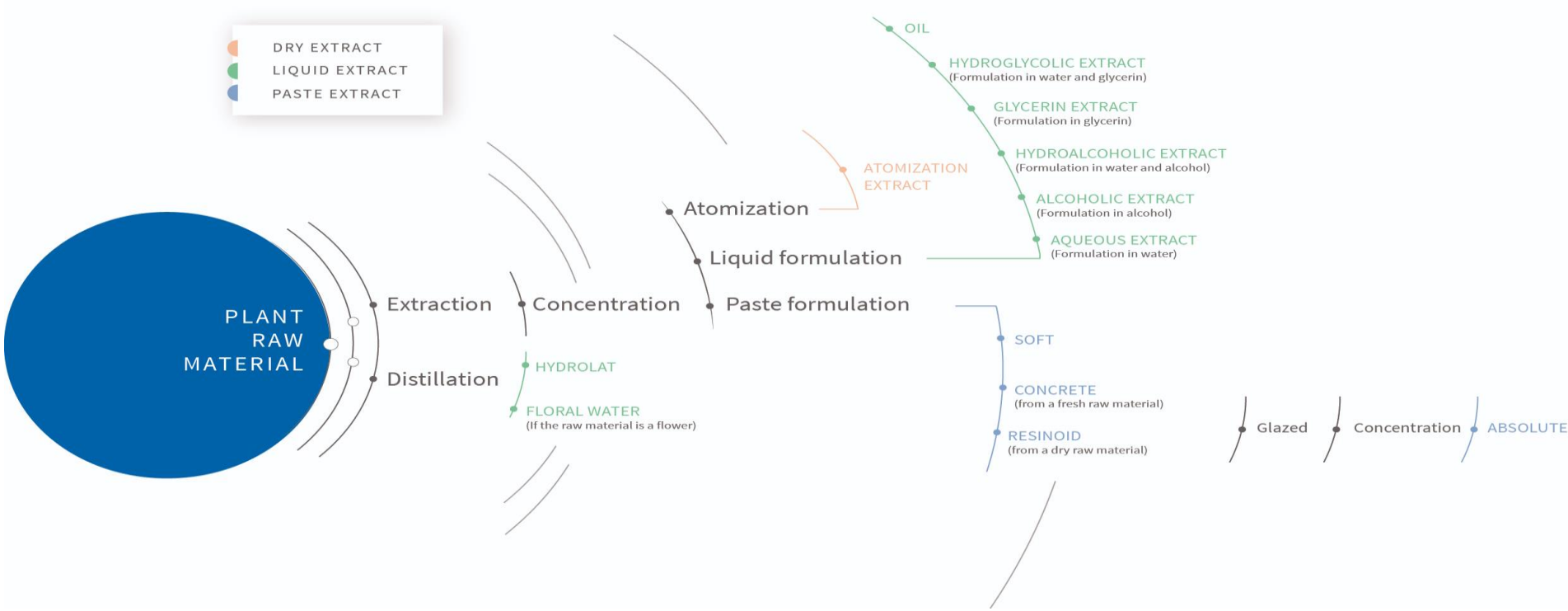
-Valeriana raíz polvo valorado 0,17% ácido valerénico

-Extracto de Valeriana 1:1, 4:1, 5:1, 10:1

-Extracto de Valeriana valorado 0,4% ácido valerénico

-Extracto de Valeriana valorado 0,8% ácido valerénico

-Extracto de Valeriana 0,8% Valeroselect®



QUALITY ASPECTS

Manufacturing

The worldwide unstandardized approach to nutraceutical regulation puts a large responsibility on supplement manufacturers to ensure a high level of quality controls to avoid endangering consumers

While specific regulations may vary by country, manufacturers should always take responsibility for traceability and quality control throughout the entire procedure.

• Manufacturing – Abiding by the World Health Organization's Good Manufacturing Processes (GMP) ensures that facilities maintain clean work areas, work to prevent cross-contamination, follow clearly defined processes, etc.

Manufacturers who successfully undergo third-party evaluations shall receive a certification.

Quality Assurance I

Many risks can be mitigated with thorough testing at each step, including but not limited to:

• Formula – trace the list of finalized ingredients as functional, repeatable measurement of the level present for each.

• Ingredients – Testing must begin with pathogen detection (and identification), and quality indicators enumeration for raw materials and ingredients.

• End-products Testing (Required & Non-Required) – In cases where rigorous testing is not required, manufacturers are responsible for purity, efficacy, and allergen testing.

Is this really different than pharma?

Quality Assurance II

Another important additional requirement is compliance with Hazard Analysis and Critical Control Points (HACCP). This is because it demonstrates that your natural ingredients are of high quality. Thus, consider aiming for compliance with HACCP as it will give you an advantage when you are seeking to enter the European market.

A second common additional buyer requirement from European buyers of natural ingredients is certification of a food management system based on HACCP. This is because having certification suggests high quality of natural ingredients for health products. You should therefore consider obtaining certification, with the most relevant being:

- International Organization for Standardization (ISO) 22000 food safety management system certification and ISO 9001:2015 and quality management systems certification
- Food Safety System Certification (FSSC 22000) which is based on ISO 22000 and is aimed specifically at food manufacturers.
- International Featured Standards (IFS) which provide several standards concerning food safety.

Quality Control

Most Common routine tests are:

•**Physical characteristics** (visual, color, odor, taste, density, mesh size)

•**Identity** (matching an ingredient in a pass/fail fashion to a particular species of botanical or herb, or a chemical purity test)

•**Potency** (concentration of active or marker compounds)

•**Purity** (absence of impurities such as moisture, microbiology, pathogens, heavy metals, residual solvents, pesticides, mycotoxins)

Also, labeling must be checked for proper:

- Labeling info
- Batch number
- Expiration date

Assay: Extracts

-Valeriana raíz polvo

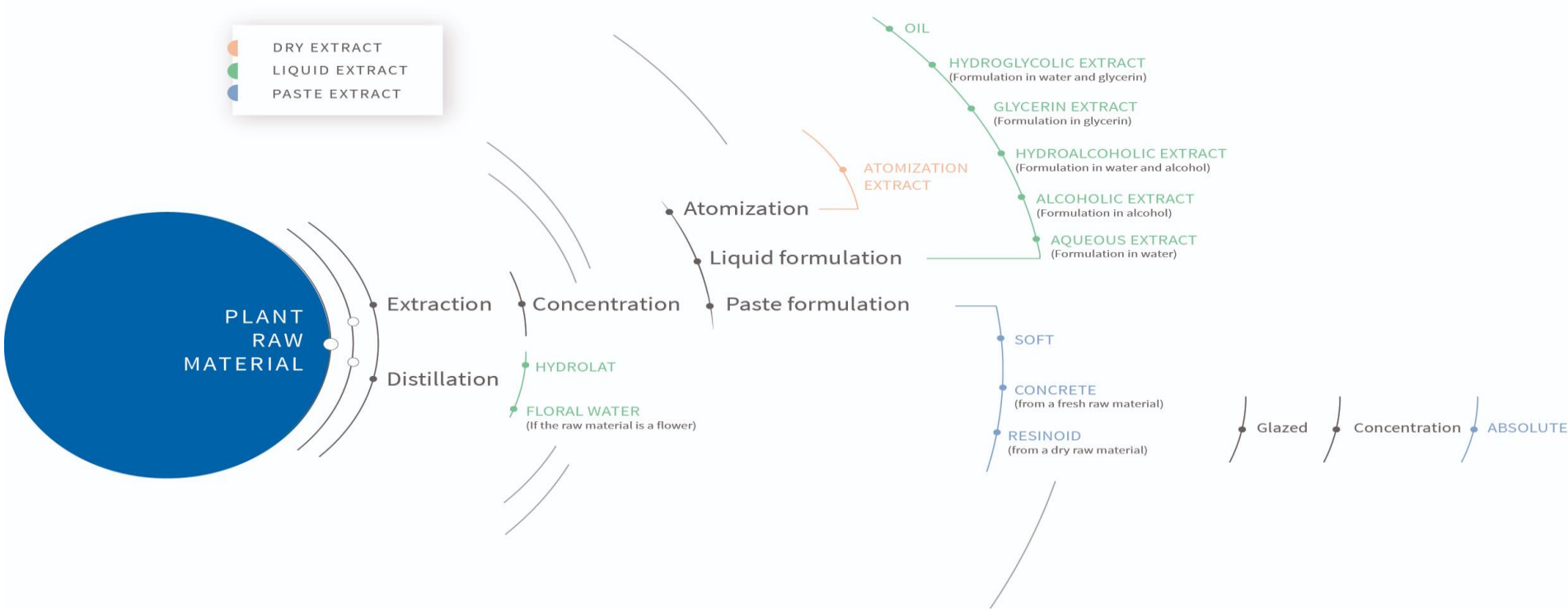
-Valeriana raíz polvo valorado 0,17% ácido valerénico

-Extracto de Valeriana 1:1, 4:1, 5:1, 10:1

-Extracto de Valeriana valorado 0,4% ácido valerénico

-Extracto de Valeriana valorado 0,8% ácido valerénico

-Extracto de Valeriana 0,8% Valeroselect®



Maximum levels for contaminants

Maximum levels for certain contaminants:

There are some maximum levels harmonized within the EU.

- Among others, the maximum levels for:
- Lead
- Cadmium
- Mercury
- PCB
- dioxin and polycyclic aromatic hydrocarbon (PAH)
- Ethylene Oxide

...are relevant for food supplements.

See Regulation (EC) No 1881/2006 setting maximum levels for certain contaminants in foodstuffs.

PHARMACEUTICALS VS. NUTRACEUTICAL???

Are they so different?

- Market Channel?
- Regulatory?
- Quality ?
- Formulation & Development?
- Stability standards?
- Manufacturing?
- ???

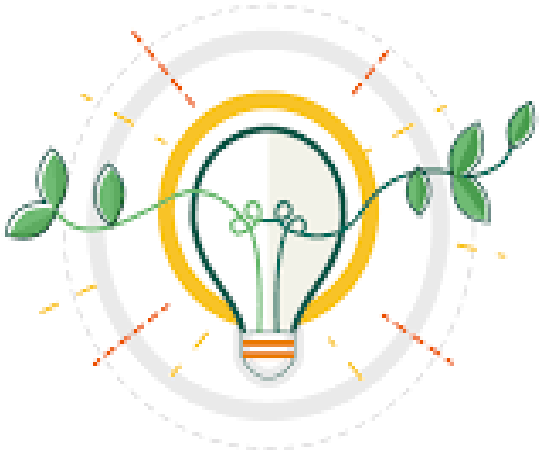
So, what is really important?

- There is some overlap in quality management systems and specifications/requirements for substances sold for use as food supplements, and pharma excipients, but many significant differences remain.

- No single quality management certification satisfies ingredient requirements for the two uses. Thus, manufacturers who supply into two or more of these markets need to understand and implement quality management system requirements to meet each of the markets they serve.

- Make sure that your supplier is reliable and does their homework!

INNOVATION



Innovation needs & trends I

Nutraceuticals market is growing at a higher rate than pharmaceuticals.

Here are some of the biggest trends in innovation for the nutraceutical oral solid dosage forms market:

EXCIPENT NEW TRENDS

1. Within nutraceutical OSDFs, the capsule form is expected to grow at a higher rate.

2. Despite the growing popularity of clean-label supplements, there is no definition or regulations provided and the meaning of clean label is usually defined by individual brand owners or manufacturers.

3. Usually, the most new demands on products are gluten-free, vegetarian/vegan, Kosher and Halal, non-GMO, organic, and free of artificial colors/preservatives.

Innovation needs & trends II

4. Nutraceuticals are more easily available than they were over a decade ago, with a substantial presence in both online stores and physical stores. Online is the most preferred nutraceutical channel.

5. Personalized interactive tools offered for free by online retailers help create a customized list of nutraceuticals based on the condition and needs of the consumer.

6. Personalized nutrition is also an emerging trend in the nutraceutical market, particularly in Europe. In most cases, it is related to offering select micronutrient combinations with individual dosages according to various needs.

Increasing Focus to Develop Quality Nutritional Products

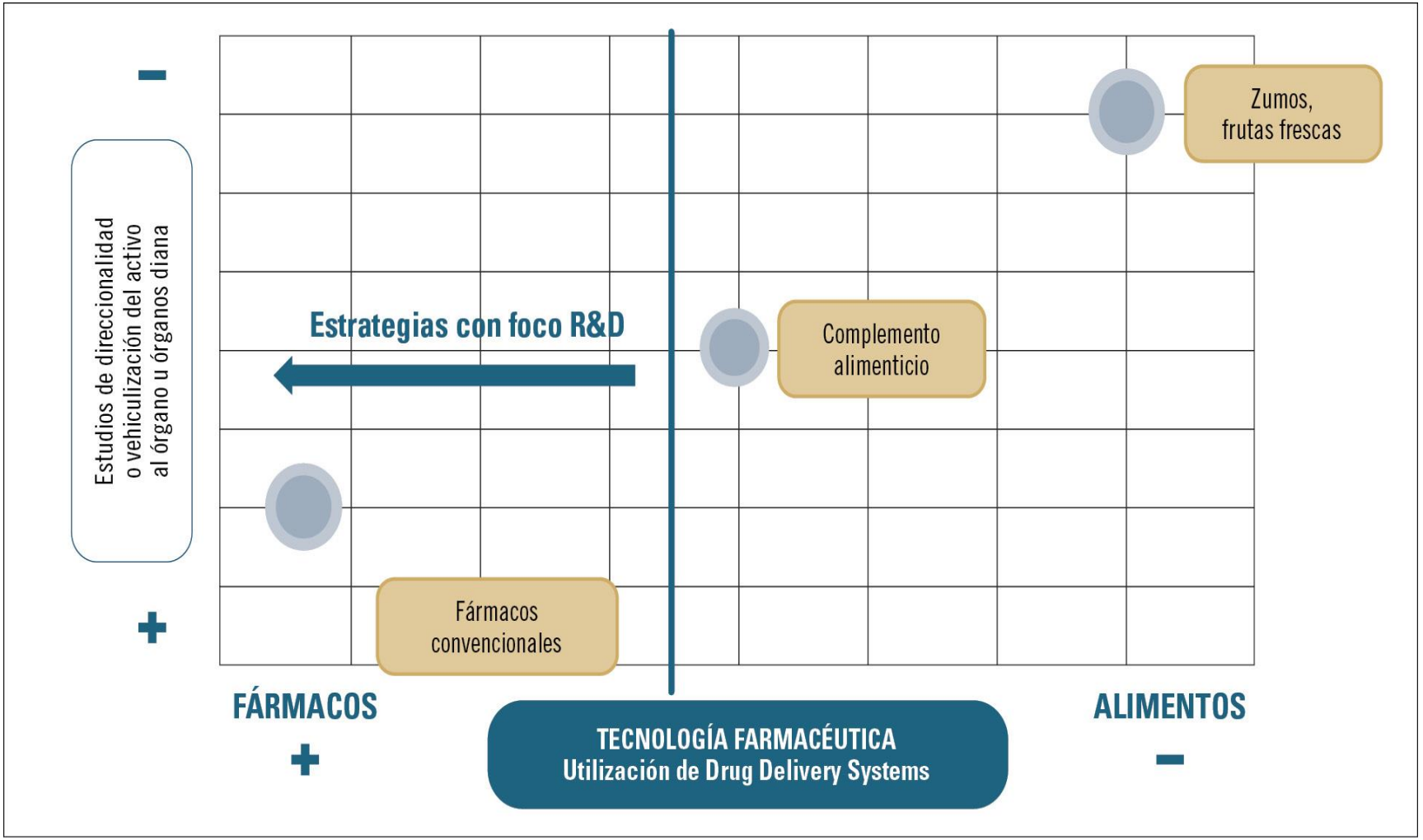
Increasing Demand for Personalized Dietary Supplements

Increasing Adoption of Plant based Diet

Increasing Focus on Consumption of Nutritious Diet

Increasing Prevalence of Lifestyle Diseases

How to differentiate my product



How to differentiate my product

- New packaging, in line with needs/trends….but care for stability!
- Use of Novel Foods
- Perform Clinical trials on your product
- Use Actives with proven clinical trials
- Use enhanced or complex pharmaceutical technology tools (retard, bioenhancers, gastroresistant…)

Nutraceuticals Market

2021 - 2030

Market by Region, 2020

Market By Type Revenue 2020

- Dietary Supplements
- Functional Beverages
- Functional Food
- Personal Care

Key Pointers

Increased aoption of fortified food owing to the growing health consciousness amongst consumers

Increasing incidences of chronic diseases

Strict government regulations on food fortification

Market Size

(USD Billion)

MARKET TRENDS: Spain

Empresas alimentarias inscritas en el RGSEAA

(Registro General Sanitario de Empresas Alimentarias y Alimentos)

Actividad: Complementos Alimenticios

Año 2014: 1.427 empresas

Año 2019: 2.002 empresas

+ 40,3%

Fabricantes

Año 2014: 175

Año 2019: 267

+ 52,6%

Distribuidores

Año 2014: 744

Año 2019: 841

+ 13%

Formamos parte de una gran industria a nivel mundial

En las últimas dos décadas, el mercado de los complementos alimenticios se ha fortalecido en todo el mundo. De hecho, su valor se ha **duplicado** desde 1999.

Año 1999: 49,1 mil millones $

Año 2020*: 140,3, mil millones $

Fuente: Nutrition Business Journal

**Dietary Supplements Market Size & Trends Report, 2021-2028*

Thanks for your attention!