7th Science to Market - "Leveraging Synergies“

Medicines, medical devices and other healthcare products – differing regulatory systems

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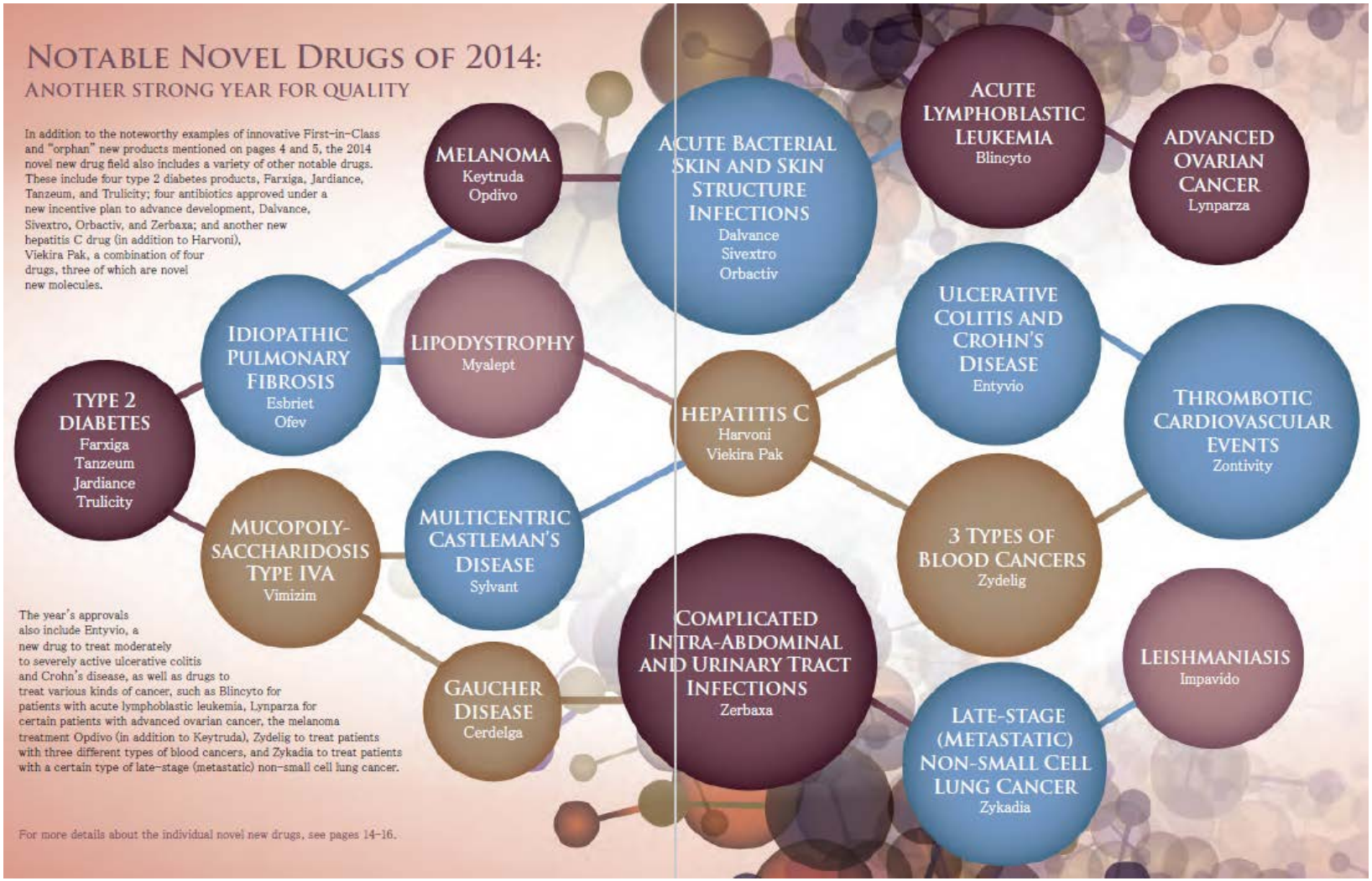
Overview

Legislative Framework

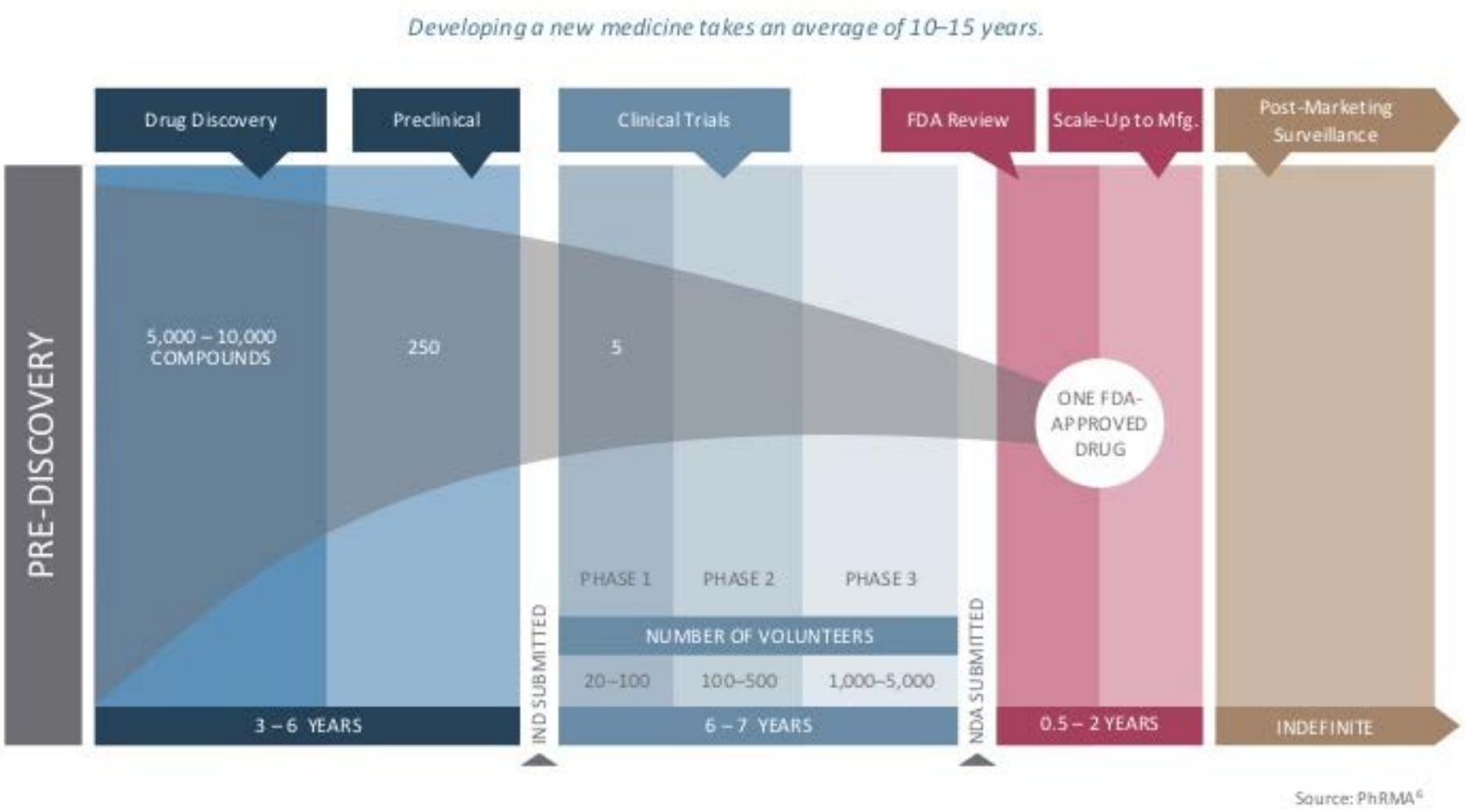
Product Examples

Considerations

- **Medicinal Products**
- **Medical Devices**
- **Biocides**
- **Food Supplements**
- **Cosmetics**



Drug Development Process



Drug Development Costs:
Tufts Center for the Study of Drug Development

The Cost of Developing a New Drug

Estimated Re-creation of the Tufts CSDD 2014 Model

Inputs in Blue

Cost of capital
11%

STAGE	Survival rates of projects in phase	Average cost per phase per project ($M)	Number of Cmpds/Projects Required at Stage Entry	Total cost, including paying for failures ($M)	Duration (yrs)	Capitalized (time-adjusted) Value at launch ($M)
Discovery	50%	$ 8	24.5	$196	1.5	539.9
Preclinical	69%	$ 10	12.2	$122	1.5	290.5
Phase I	60%	$ 20	8.5	$169	1.6	343.4
Phase II	36%	$ 80	5.0	$402	2.5	666.2
Phase III	62%	$ 300	1.8	$536	2.5	691.4
Registration	90%	$ 10	1.1	$11	1.3	13.4
Market			1			
TOTAL	8.2%	$428		$1,437	10.9	$2,545

Costs calculations are based on 10 companies and 106 randomly selected drugs

The $2,5 billion per approved compound is based on estimated:

- **Average cost of $1,4 billion**
- **Time costs (expected returns that investors forego while a drug is in development) of $1,1 billion**

http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study

EU Legal Framework: Medicinal Products for Human

The **EU legal framework** for medicinal products for human use is intended to ensure a high level of public health protection and to promote the functioning of the internal market, with measures which moreover encourage innovation.

European Medicines Agency (EMA)

Community authorization procedures (centralized, mutual recognition) are in place since the mid-90s. The system is supported by a Community regulatory agency in charge of providing the EU institutions with scientific advice on medicinal products:

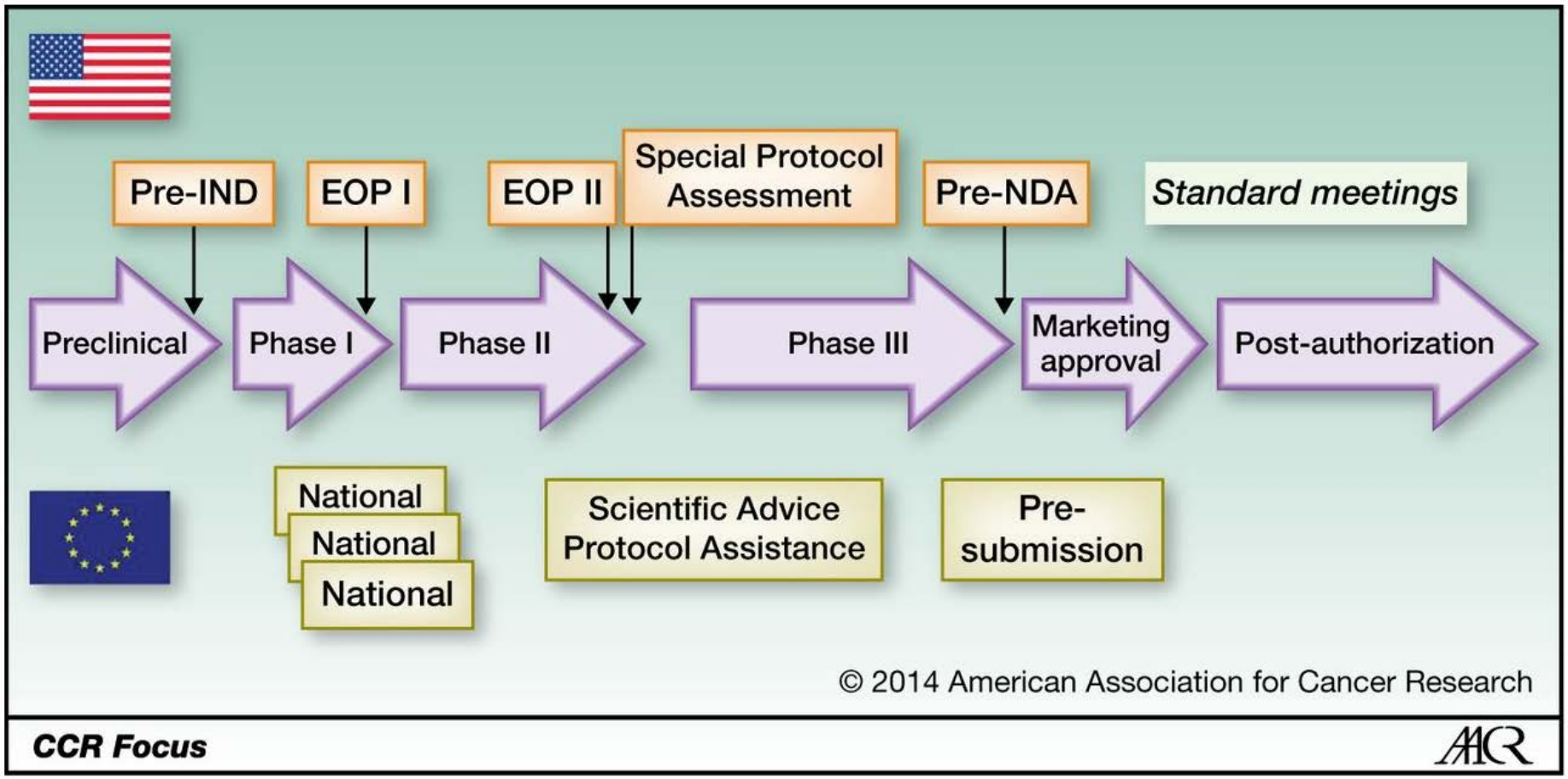
The requirements and procedures for the marketing authorization for medicinal products for human use:

- **Directive 2001/83/EC**
- **Regulation (EC) No 726/2004**

Community legislation also provides for common rules for the conduct of clinical trials (the investigations in humans intended to discover or verify the effects of medicinal products before their authorization) in the EU.

In addition, various rules have been adopted to address the particularities of certain types of medicinal products and promote research in specific areas:

- **orphan medicinal products** (Regulation (EC) No 141/2000)
- **medicinal products for children** (Regulation (EC) No 1901/2006)
- **advanced therapy medicinal products** (Regulation (EC) No 1394/2007)


Pre-IND
EOP I
EOP II
Special Protocol Assessment
Pre-NDA
Standard meetings
Preclinical
Phase I
Phase II
Phase III
Marketing approval
Post-authorization
National
National
National
Scientific Advice Protocol Assistance
Pre-submission
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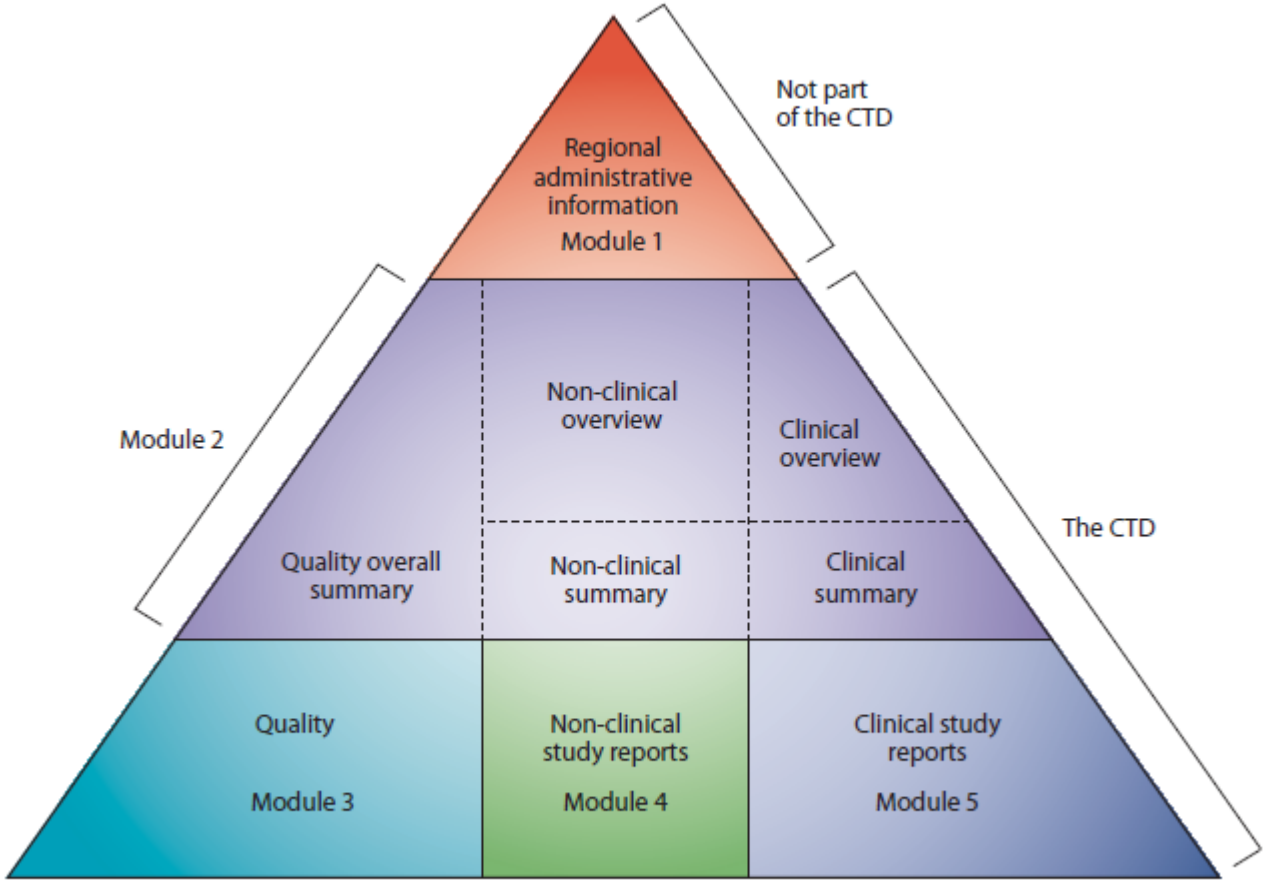
CCR Focus

ICH CTD (Common Technical Document)

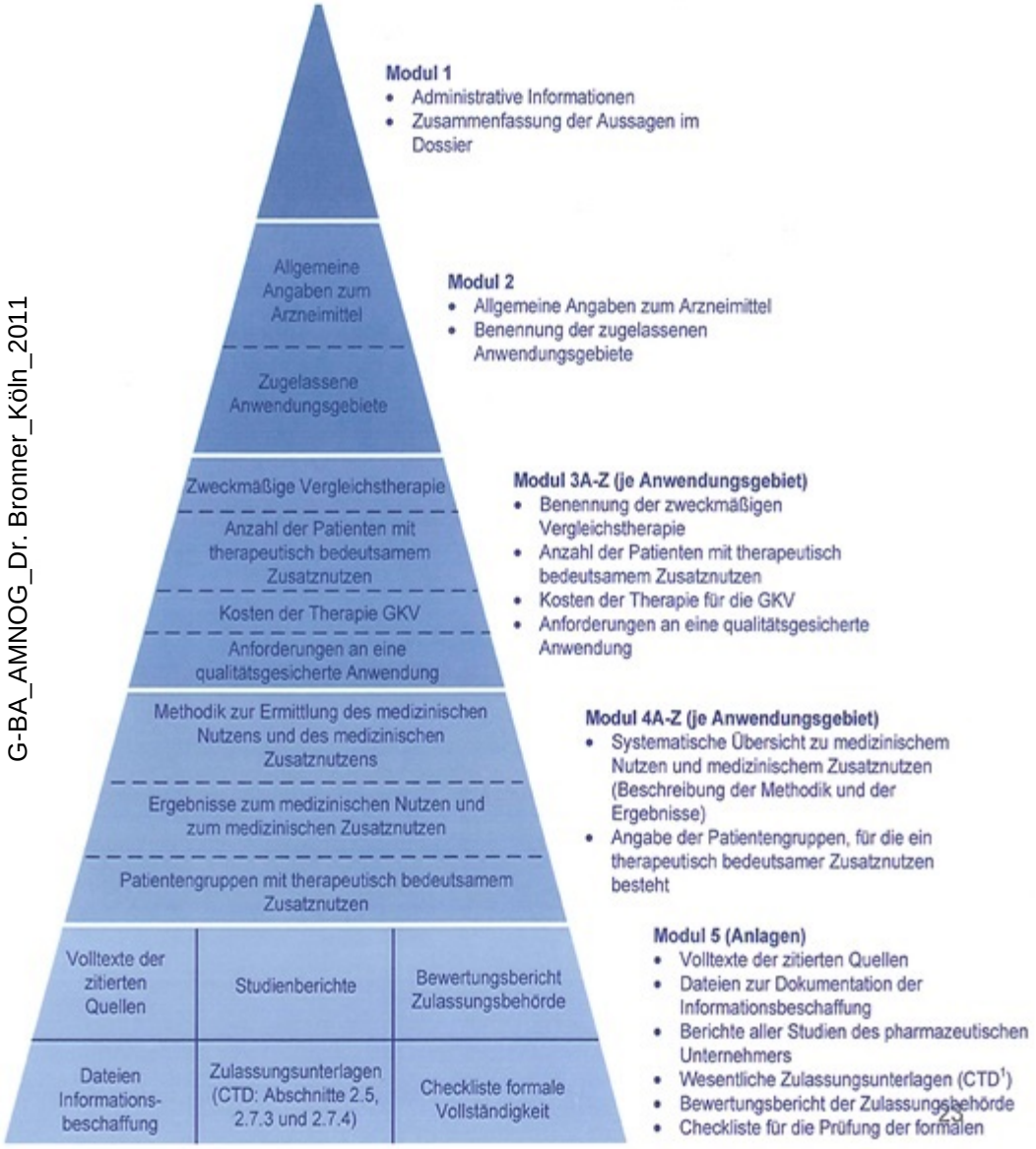


The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/CTD_triangle.pdf

Cost-Benefit Analysis for Prescriptive Drugs in Germany

Basis for the Price Finding Approach



MODULE 1
Administrative information

MODULE 2
Designation of approved application areas

MODULE 3
- **Designation of the appropriate comparative therapy**
- **Treatment cost for legal health insurances**
- **Requirements for a quality-assured application**

MODULE 4
- **Systematic overview of a medical treatment benefit (i.e. methodology and results)**
- **Specifications of patient subpopulations with significant treatment benefit**

MODULE 5
- **References and documentation data etc.**
- **Assessment report (i.e. EPAR)**

G-BA_AMNOG_Dr. Bronner_Köln_2011

Medical Devices (EU)

MDD Article 1, §2 (a): '**medical device**' means any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software **intended by its manufacturer** to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of

- diagnosis, prevention, monitoring, treatment or alleviation of a disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,

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

EU Regulatory Framework for Medical Devices

Principle of the procedure

Adoption of a directive by the European Parliament and Council

Transposition of the directive into national law in each EU member state

- National Law
- Additional regulations on the national law

Example Medical Device in Germany

Directive 93/42/EEC
Medical Device Directive (MDD)

Transposition of MDD into German Law

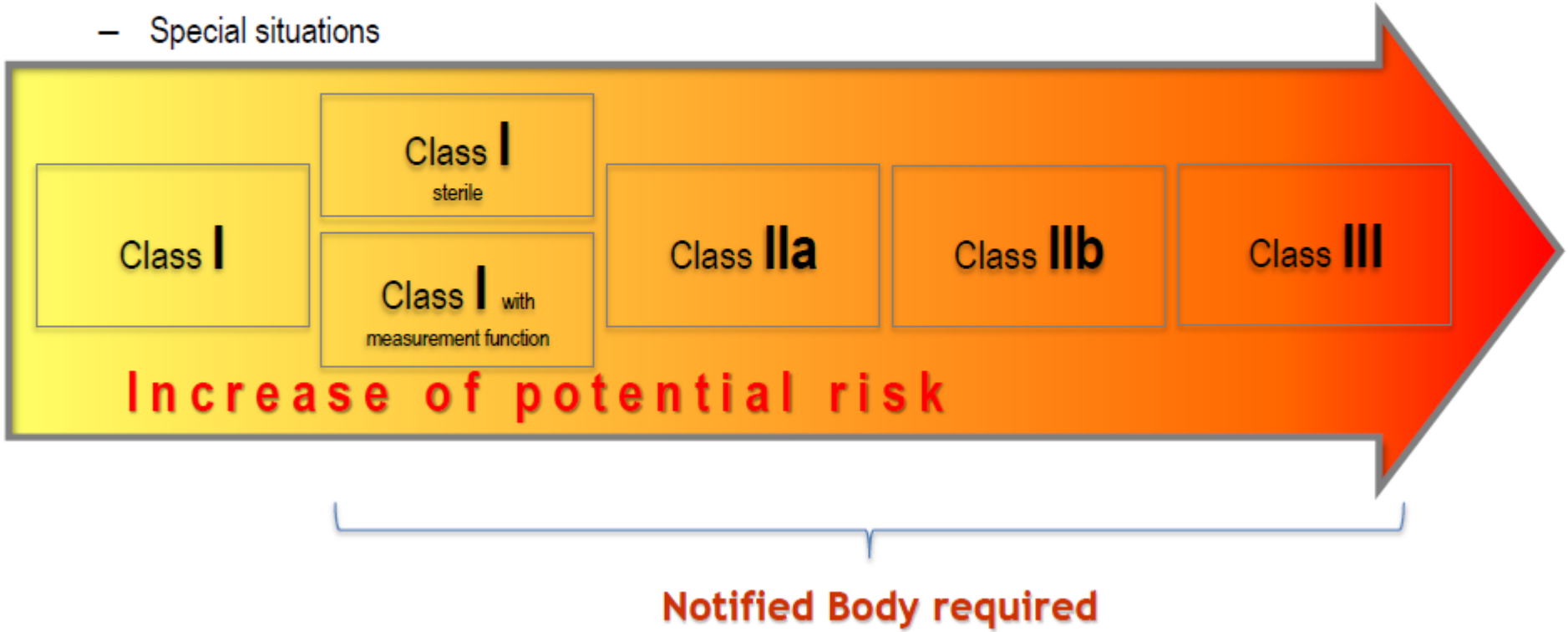
- Medizinproduktegesetz *1
  (German Medical Device act)
- Regulations on the Medical Device Act (e.g. MPSV)

http://www.isfacongress.com/wp-content/uploads/2015/05/Regulatory-Process-For-Medical-Devices-In-Europe-Current-status-and-upcoming-revised-regulation.pdf

Medical Device Risk Classes According to EU MD

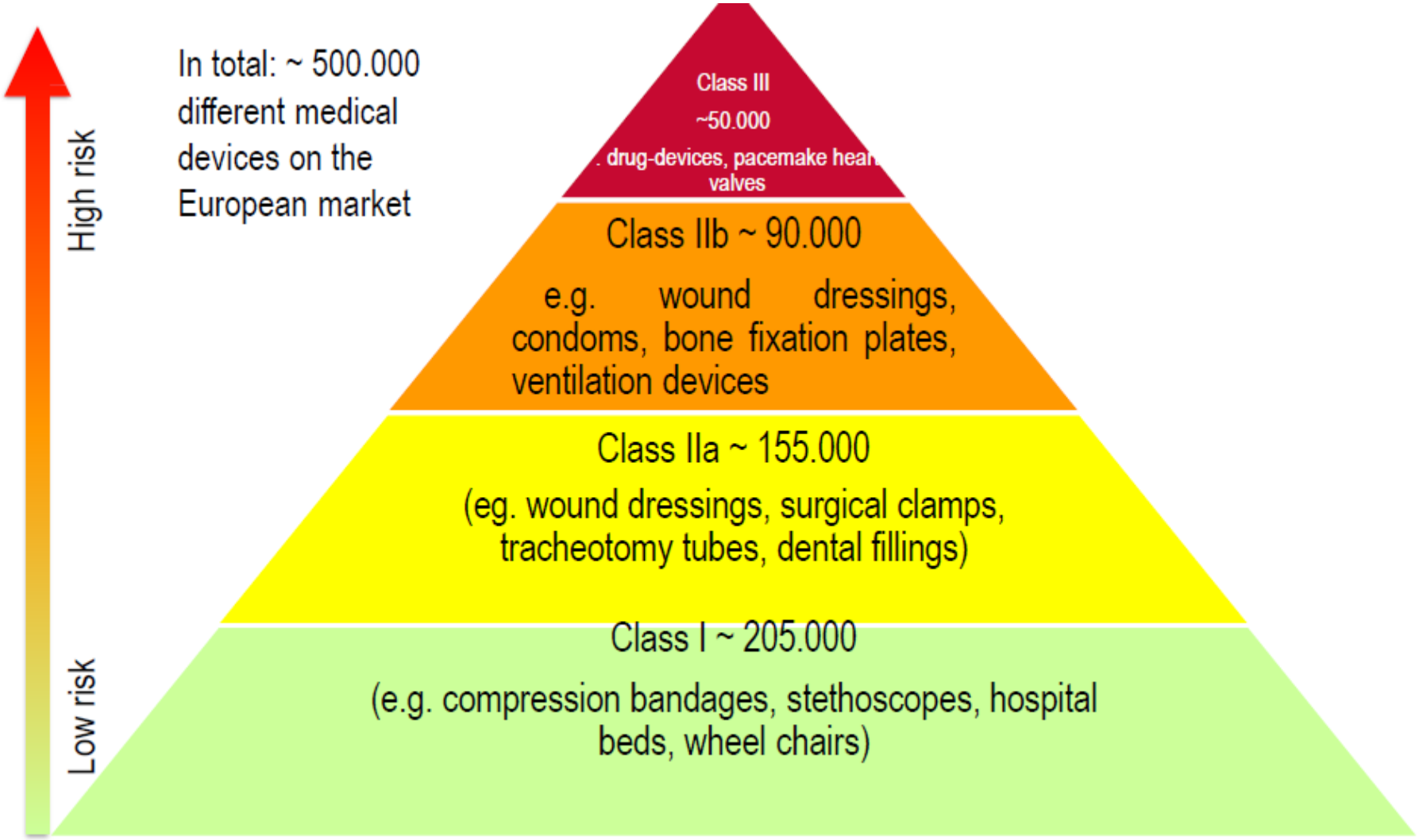
- Annex IX, 18 rules based on:
  - **Intended use**
  - Duration of contact
  - Degree of invasiveness
  - Special situations

The classification of the MD determines the conformity assessment route selected by the manufacturer



http://www.isfacongress.com/wp-content/uploads/2015/05/Regulatory-Process-For-Medical-Devices-In-Europe-Current-status-and-upcoming-revised-regulation.pdf

Medical Devices in Europe by Risk Class



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Essential Requirements for Medical Devices

General medical device requirements:

- **Design and construction requirements**
- **Chemical, physical and biological properties**
- **Information supplied by the manufacturer on the label and in the instructions for use**

Clinical Data to Address Safety/Efficacy of MDs

- **Clinical investigation of the medical device**
- **Clinical investigation or other studies reported in the scientific literature, of a similar device with demonstrated equivalence**
- **Published and/or unpublished reports on other clinical experiences of either the respective device or a similar device with shown equivalence**
- **Compilation of all information into a Clinical Evaluation Report**

How to realize clinical studies is not regulated by MD directive but different local regulations are in place.

EU Biocides – Basic Concepts

- **Active substance:**

  A substance that has an action on or against harmful organisms

- **Harmful organism:**
  - An organism (including pathogenic agents) with an unwanted presence or a detrimental effects on humans, on animals or on the environment
  - The products (that these organism use or produce) with detrimental effect on humans, on animals or on the environment

- **Biocidal products:**

  22 product types (Annex V)

EU Biocides: Main Group and Product Types

Disinfectants
human hygiene (1), public health (2), veterinary (3), food and feed areas (4), drinking water (5)

Preservatives
in-can (6), film (7), wood (8), fibre (9), construction material (10), liquid cooling (11), slimicides (12), metal working fluids (13)

Pest control
rodenticides (14), avicides (15), molluscicides (16), piscicides (17), insecticides (18), repellents (19) and other invertebrates (20)

Other
antifouling paints or coatings against sessile organisms like barnacles or mussels (21), embalming/taxidermist fluids (22)

echa.europa.eu/de

EU Biocides - Directive and Regulation

New definitions include

- **Requirements for treated articles**
- **Hazard-based exclusion and substitution**
- **Detailed procedure for mutual recognition**
- ***Union authorisation*** **of biocidal products**
  - ✓ **Products with similar conditions of use**
    - **Excluded:**
    - **Products to control rodents, birds, fish, and other vertebrates (PTs 14, 15, 17 and 20)**
    - **Antifouling products (PT 21)**
- **Harmonised "*summary of the product characteristics*" for authorisation**

Directive	Regulation
98/8/EC	EU 528/2012
Annex I-inclusion	Approval
Annex I	List of approved substances
Annex IA	Annex I
Low-risk products	Products eligible for the simplified procedure
Frame formulation	Biocidal product family

EU: Food Supplements Legislation

Novel Foods
Reg EC/258/97
Pre-marketing approval procedure for novel ingredient

General Food Law
Reg EC/852/2004
General food safety requirements

Fortification
Reg EC/1925/2006
Risk assessment and management of substances with harmful effects

Pesticides residues
Reg EC/396/2005
Maximum residue levels

Food Supplements Law
Dir 2002/46/46
Forms and levels vitamins/minerals

Additives legislation
Dir 89/1007/EEC
Pre-marketing approval procedures allowed additives including sweeteners and colourings (conditions of use)

Food Hygiene
Reg EC/852/2004
Rules of hygiene production/micro-biological criteria

Health Claims
Reg EC/1924/2006
Pre-marketing approval for nutrition and health claims

Labelling
Dir 2000/13/EC
How to label content and composition
Quantitative ingredient declaration
Allergen labelling

Contaminants
Reg EC/188/2006
Maximun levels of selected contaminants in ingredients that can be used in foods

Main EU Legislation for Cosmetics

The new EU Regulation 1223/2009 (Cosmetics Regulation) has been in force since 2013.

It strengthens the safety of cosmetic products and streamlines the framework for all operators in the sector.

The new Regulation replaces Directive 76/768/EC.

<u>The most significant changes introduced by the new Cosmetics Regulation include:</u>

- **Strengthened safety requirements for cosmetic products**
- **Introduction of the notion of "responsible person"**
- **Centralised notification of all cosmetic products placed on the EU market**
- **Introduction of a reporting system for serious undesirable effects (SUE)**
- **New rules for the use of nanomaterials in cosmetic products**

The EU Cosmetics Regulation

Restrictions for Certain Substances and Special Provisions

- **CMR substances (Carcinogenic, Mutagenic or toxic for Reproduction)**

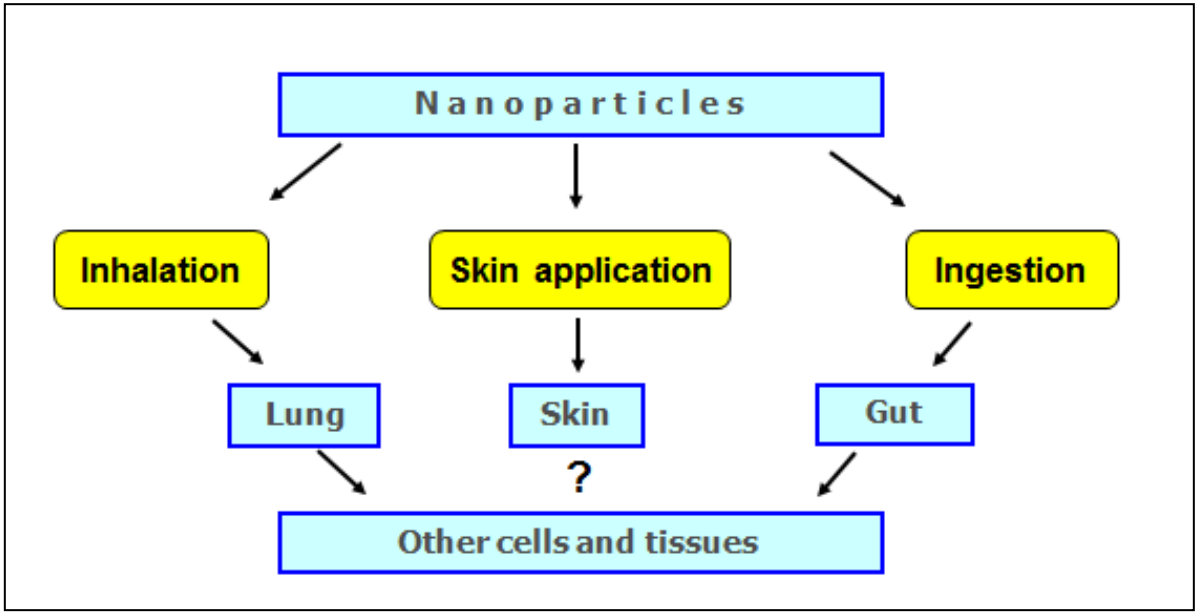
  CMR classification (regulation Nr. 1272/2008)
  - ✓ **Annex II - list of 1328 prohibited substances**
  - ✓ **Annex III - list of 256 restricted substances**

- **Also prohibited:**
  - ✓ **Certain colorants (other than those in Annex IV),**
  - ✓ **Preservatives (other than those in Annex V) and**
  - ✓ **UV-filters (other than those in Annex VI)**
  - ✓ **Substances recognised as Carcinogenic, Mutagenic or toxic for Reproduction (CMR), apart from exceptional cases**

  - ✓ **Nanomaterials must be labeled in the list of ingredients with the word "nano" in brackets following the name of the substance.**

Nanomaterials – Safety Concerns

Nanomaterial means an insoluble or bio-persistant and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm."



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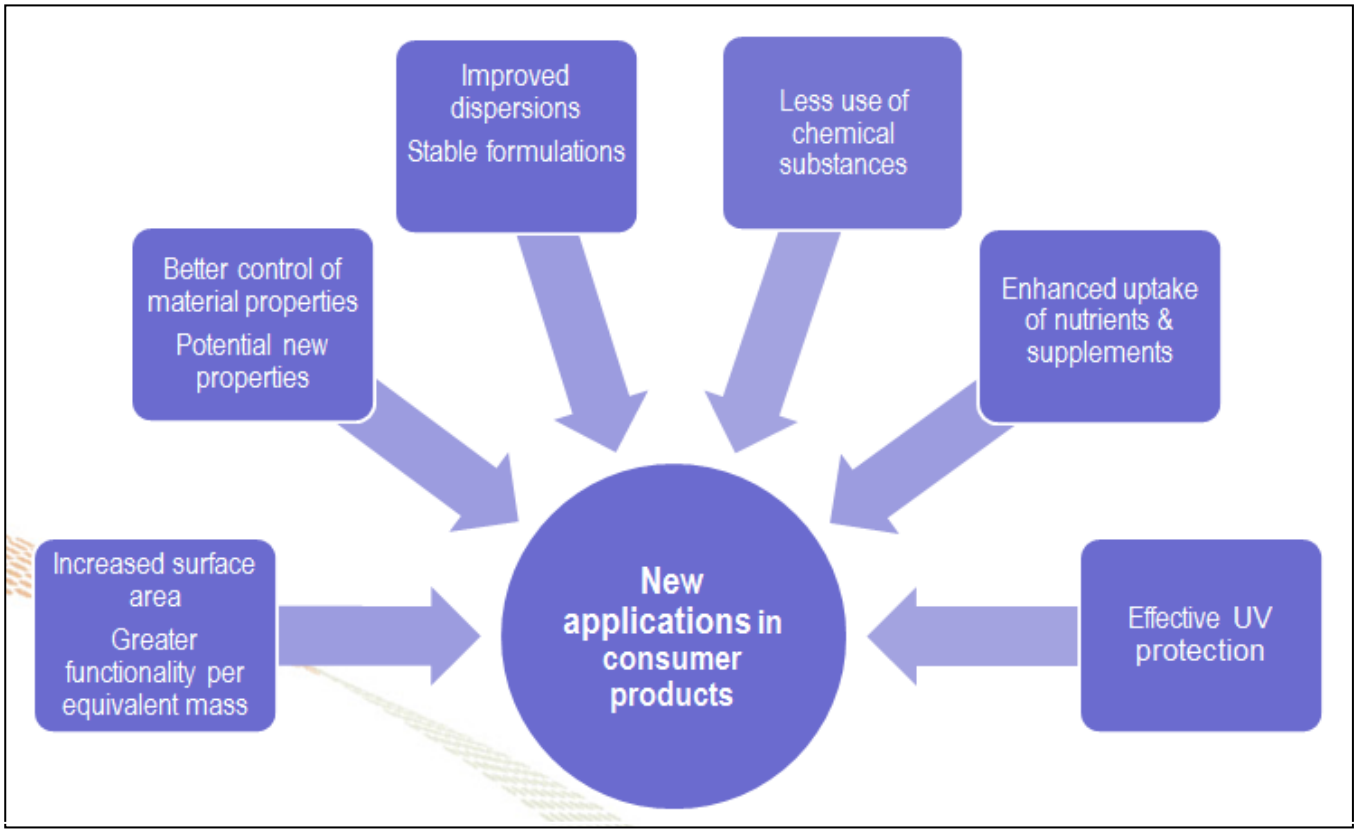
- **Nanoparticles may cross membrane barriers and reach new targets in the body**
- **Nanoparticles may interact with biological entities close to the molecular level**
- **Exposure to insoluble/ bio-persistent nanoparticles may cause concerns over adverse health effects**

Nano-sized Cosmetic Ingredients



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- **Used for better dispersibility, anti-microbial or anti-oxidant properties, effective UV-protection, visual clarity of sunscreen formulations etc.**
- **A growing range of products worldwide. Only a few products currently in Europe – mainly sunscreens containing nano UV filters**

Thank you for

your

attention!

Any questions?