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NUTRITION HEALTH BIOTECHNOLOGY

*Our Mission:*
*Bring the proof of Health Effect*

# Health Claim Dossier : How To Ensure You Have The Right Strategy In Place

*Dr Christophe Ripoll, Executive VP ,CSO*

**Allégations nutritionnelles et de santé : état des lieux et perspectives**

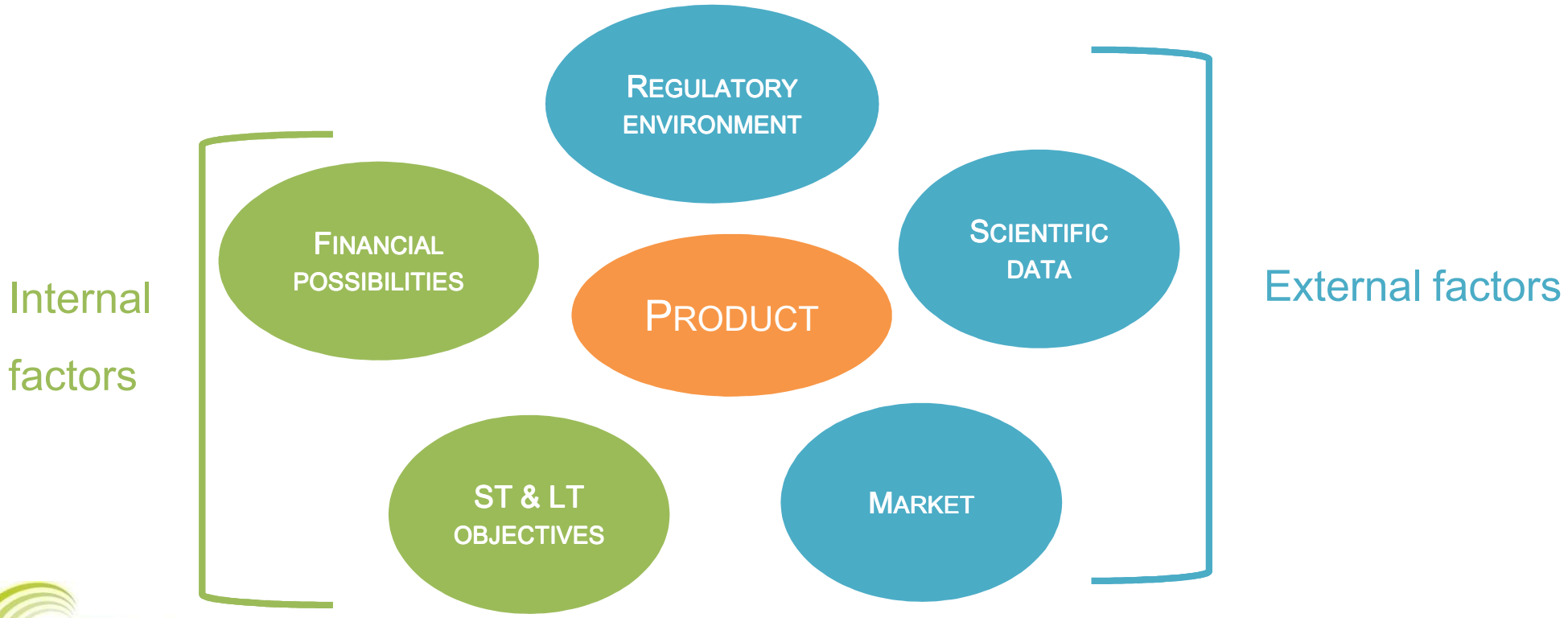
*16 Novembre 2011 - Université de Liège Sart-Tilman*

# *Product development for the Nutrition & health market*

- First step in the development of a product for the Nutrition & health market

= **identify potential claims opportunities** and **develop a specific and focused R&D strategy**

- How? Analysis of the global product environment



# *Food industry & health Communication issues*

Communication on health & well-being (B2C)

Regulation EC 1924/2006

Topic not considered as related to health

**Wellness, Cosmetics etc**

+/- MKT study
+/- POC study

Claims (e.g skin elasticity)

Topic considered as related to health

Clinical trial substantiation strategy
POC + POE studies

efsa
European Food Safety Authority

EU Commission

Health Claims

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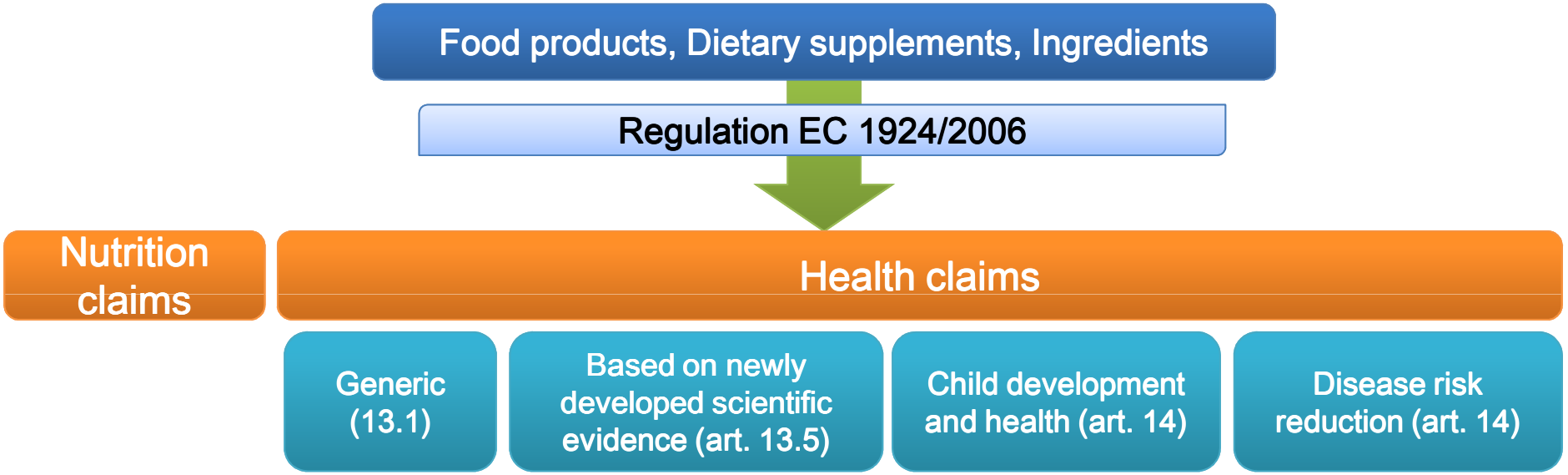
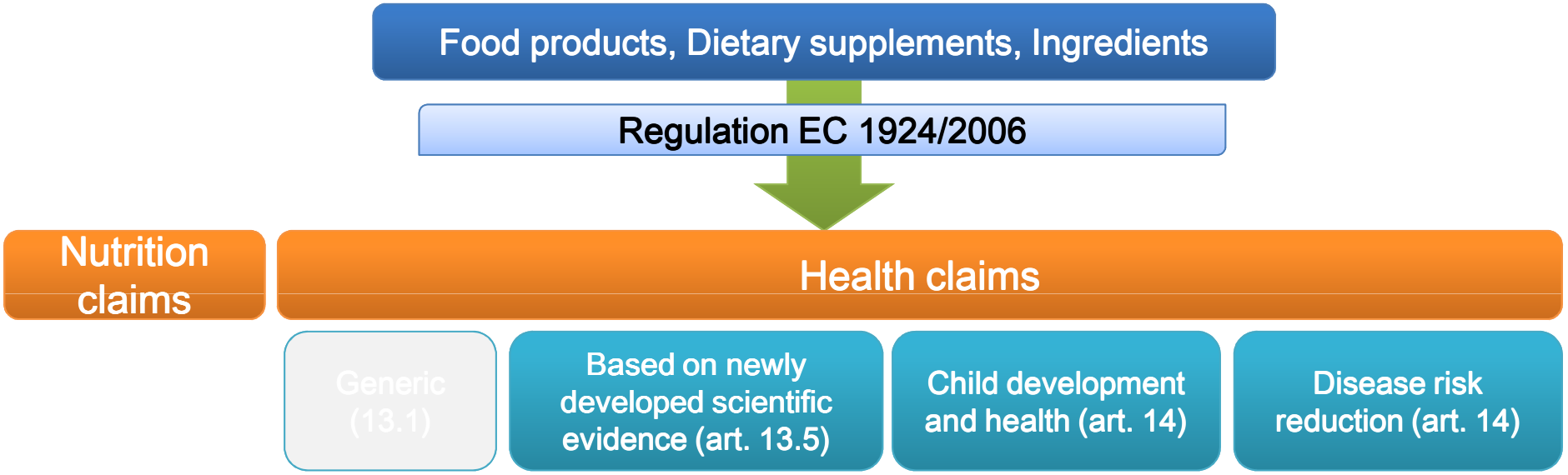
# *EC 1924/2006 regulation*

- Different types of claims …



# *EC 1924/2006 regulation*




- Scientific data & clinical trials needed to substantiate the application dossiers

# *Health claim : how to start ?*

Scientific and regulatory analysis

In vitro, in vivo, Clinical trials published data

Non-published Scientific data Internal reasearch

EFSA databases

Scientific consensus

Claim wording & positioning

Scientific admissibility of the dossier / Gap analysis

EFSA route Regulatory Health Claim dossier writing (model EFSA)

Additional research /Clinical trial set up

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# *Analysis of the scientific consensus (I)*

- Systematic Review of the Totality of Evidence
  - Preclinical & clinical studies directly linked to the claim
  - Set -up a pre-defined and reproducible methodology
  - Explicit definitions of terminology used
  - Define inclusion and exclusion criteria against all
  - Indentify the appropriate scientific database
  - Search, select and reference  the list of the selected papers
  - Review and evaluate in an objective and unbiased manner
  - Summarize data

# *Analysis of the scientific consensus (II)*

- Evaluation of the strengths and weaknesses of the scientific data

Table 4
Summary of phytoestrogen clinical studies

| | Positive results | Total |
|---|---|---|
| *Clinical endpoints* | | |
| Maintaining bone density | 11 | 15 |
| Relief menopause symptoms | 4 | 17 |
| Cardiovascular benefit | 25 | 38 |
| Cancer prevention | 7 | 13 |
| Hormone levels/menstrual cycle | 12 | 19 |
| Effect on hormones in men | 0 | 1 |
| Immune system | 1 | 1 |
| Neurological | 5 | 5 |
| Total[a] | 64 | 105 |
| *Type of phytoestrogens* | | |
| Soy isoflavonoids | 41 | 70 |
| Clover isoflavonoids | 2 | 5 |
| Lignans | 15 | 23 |
| Other [b] | 3 | 4 |
| Genistein 2 | 3 | 5 |
| Ipriflavone | 1 | 1 |
| *Subjects* | | |
| Peri/post menopausal women | 42 | 70 |
| Pre menopausal women | 21 | 33 |
| Men | 7 | 16 |
| Infants | 1 | 1 |

*T. Cornwell et al. / Phytochemistry 65 (2004) 995–1016*

# Analysis of the scientific consensus (III)

| Reference | Dose and intervention duration (ID) | Population | Design | Results | Score (1-14) |
|---|---|---|---|---|---|
| **N-3 polyunsaturated fatty acids (n-3 PUFAs)** | | | | | |
| **Stammers et al, 1992** | 10 ml Cod liver oil (786 mg EPA) per day during 24 weeks | English middle-ages and old patients with OA ( Y: 49-87) N=86 | Double-blind, placebo-controlled trial | **No effect on pain and ability** compared to olive oil | **7** |
| **Cho et al, 2003** | 4 capsules per day of green-lipped mussel extract rich in n-3 PUFAs during 8 weeks | Korean patients with hip or knee OA (Y: 40-75) N=60 | Multicenter open trial | **Improvement of OA signs and symptoms** (pain VAS, joint function LFI) | **4** |
| **Avocado/soybean unsaponifiables (ASU)** | | | | | |
| **Lequesne et al, 2002** | 300 mg of Piascledine ® (capsule) during 2 years | French patients with regular pain due to primary hip OA (Y: 50-80) N=108 | Prospective, multicenter, randomized, parallel group, double blind, placebo-controlled trial | **No structural effect** (joint space width) (primary outcome),<br>**Reduction of the progression of joint space loss** in the subgroup with advanced space narrowing (post-hoc analysis)<br>**No difference for clinical parameters** (secondary outcomes) between ASU and placebo groups | **11.5** |
| **Maheu et al, 1998** | 300 mg of Piascledine ® (capsule) during 6 months + 2 month post) treatment follow up | French patients with symptomatic primary hip or knee OA (Y: 45-75) N=164 | Prospective, randomized, double-blind, placebo-controlled multicenter trial | **Decrease of LFI scores** (primary outcome) after 6 months, compared to baseline and placebo groups,<br>**Reduction of pain by VAS**, overall functional disability and patient's overall assessment efficacy<br>**No difference in NSAID consumption** except for the period ranging from 6 to 8 months,<br>**Beneficial effects measured by LFI**, **pain by VAS** and **functional disability started after 2 months** (delayed action), **Prolonged effect of ASU,** persisting 2 months after treatment discontinuation | **14** |

From Henrotin *et al*, in preparation

# *Analysis of the regulatory environment (I)*

- *Evaluation of positive and negative opinions and EFSA document guidance*

- *Overview of health claim applications :*
  - *Article 13.5 :*
    - *The* panel has received to date **59** applications, **14** have been withdrawn, **36** scientific opinions have been adopted among which **4** have received a favorable opinion
  - *Article 14 :*
    - The panel has received to date **275** applications, **109** applications have been withdrawn , **87** scientific opinions have been adopted among which **27** have received a favorable opinion

NUTRIALPHA EUROPE *Health claim DB*

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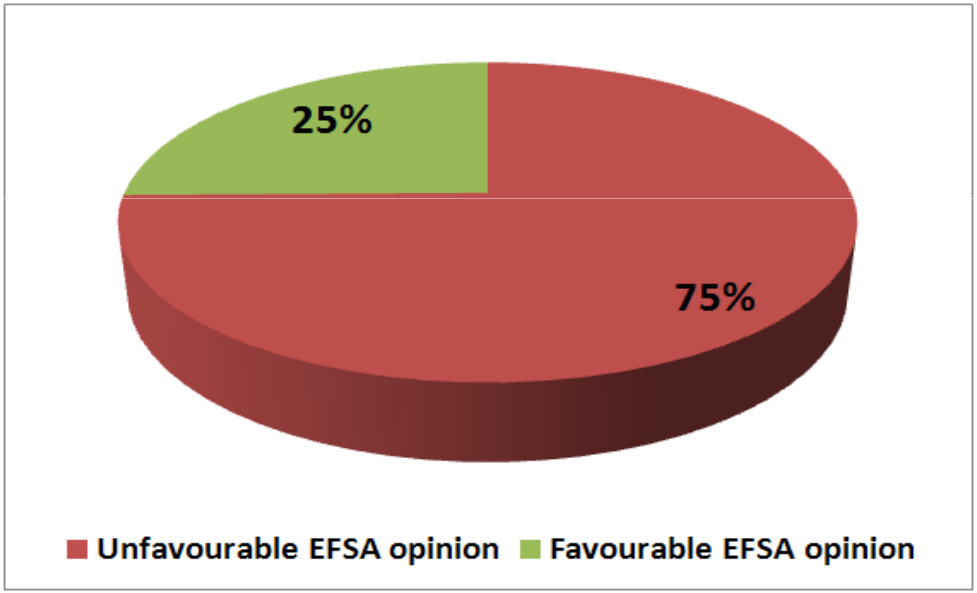
# *Analysis of the regulatory environment (II)*

- Article 13.5 & 14 evaluation by EFSA




Source: NutrialphaEurope.com

# *Art 13.5: health claims Based on newly developed scientific evidence*

- Water-soluble tomato concentrate (WSTC I and II) and platelet aggregation
- "Slowly digestible starch in starch-containing foods" and "reduction of post-prandial glycaemic responses"
- "Toothkind" drinks and reduction of tooth demineralisation
- L-tyrosine and contribution to normal synthesis of dopamine

# *Art 14 : Claim for disease risk reduction*

- **Cardiovascular health**
  - Low fat and low trans-spreadable fat rich in unsaturated and omega-3 fatty acids and reduction of LDL-cholesterol concentrations
  - Oat beta glucan and lowering blood cholesterol and reduced risk of (coronary) heart disease
  - Danacol® and blood cholesterol
  - Plant stanol esters and blood cholesterol
  - Plant Sterols and Blood Cholesterol
- **Cognitive health**
  - alpha linolenic acid and contribution to brain and nerve tissue development
- **Bone health**
  - Vitamin D and risk of falling
  - Calcium + Vitamin D3 chewing tablets and bone loss
- **Oral health**
  - Sugar free chewing gum and neutralisation of plaque acids which reduces the risk of dental caries
  - Sugar free chewing gum and reduction of tooth demineralisation which reduces the risk of dental caries
  - Xylitol chewing gum and reduction of the risk of tooth decay

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# *Art 14 : Claim for child development and health*

- **Cognitive health**
  - Thiamin and maintenance of normal neurological development
  - Iron and cognitive development of children
  - ALA and contribution to brain development
- **Bone health**
  - Dairy fresh cheese and bone growth
  - Animal protein and bone growth
  - Calcium and bone growth
  - Calcium and vitamin D and bone strength
  - Vitamin D and bone growth
- **Eye health**
  - Lipil® and visual development
  - Enfamil® Premium and visual development
  - DHA and ARA and visual development
  - Carbohydrate metabolism and diabetes
  - Thiamine and carbohydrate and energy-yielding metabolism
- **Energy metabolism**
  - Thiamine and carbohydrate and energy-yielding metabolism
- **General growth**
  - Iodine and the growth of children
  - ALA and LA and growth and development of children

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# *EFSA Guidance gut health and immunity*

- Maintaining normal immune function in population groups considered to be **at risk of immunosuppression** or **showing improvement of those symptoms and/or immune markers** may be considered appropriate.

- **Stimulation of protective antibody titres, as measured by increased numbers of individuals attaining protective levels**, could be used to substantiate a health claim on the function of the immune system related to defence against pathogens"

- **Balances your healthy intestinal flora in the context of decreasing potentially** pathogenic intestinal microorganisms might be beneficial to human health

- The numbers/proportions of bacterial groups that would constitute a "balanced/healthy" intestinal flora have not been established. **Increasing the number of any groups of bacteria is not in itself considered as beneficial.**

*EFSA Journal 2011;9(4):1984*

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Scientific consensus

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Claim wording & positioning

Scientific admissibility of the dossier / Gap analysis

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# *Scientific admissibility of the dossier / Gap analysis*

- Validation of the adequacy of the claim within the EFSA framework
- Overview on the quality and quantity of pertinent studies
- Evaluation of the pertinence of available scientific data and the targeted health claim
- Identification of strengths and weaknesses of data and set up of the complementary research if needed
- Decision on the final strategy to address (Go/NoGo, EFSA route, Non EFSA route,…)
- Set of the “needed” R&D strategy

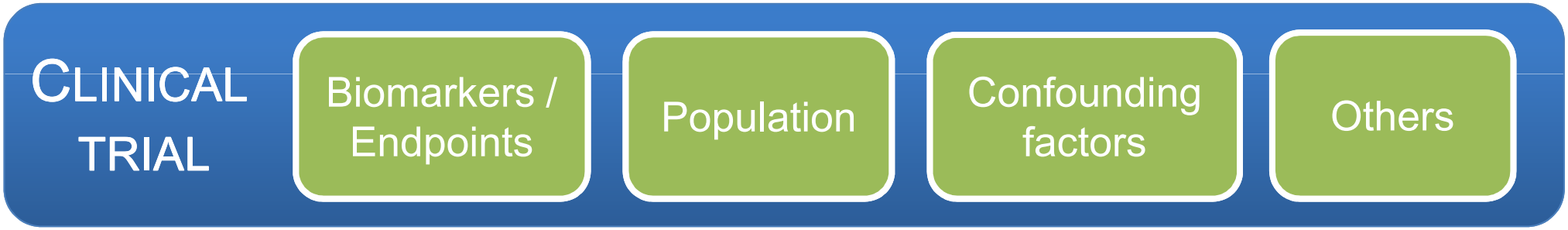
# *Building the scientific efficacy file (I)*

- Proof of efficacy in lab model – Preclinical study
  - *Objectives is to obtain relevant information that allow to :*
    - Characterize the product candidate
    - Validate health potential and biological target
    - Decipher mechanism of action
    - Evaluate active doses, way and duration of administration of the product
    - Validate biomarker or endpoint criteria

# *Building the scientific efficacy file (II)*

- Proof of efficacy in HUMAN – clinical study
  - Data on human to validate a health claim on a specific product are mandatory

- Several critical points in the clinical trial design




  - Others: statistics, monitoring tools etc

- ⇨ Need for a real emphasis on each of these critical points with adequate substantiation

# *Clinical trial design key points*

**CLINICAL TRIAL**

- Biomarkers / Endpoints
- Population
- Confounding factors
- Others

- **Biomarkers and population are indissociable = must be chosen together**

- **Examples for immunity claims**
  - Elderly show a number of immune markers decreased with ageing
    - ↘ NK cells after stimulation
    - ↘ activation lymphocytes T & B
    - ↘ CD4/CD8 ratio
    - ↗ production of certain inflammatory mediators Etc
  - From a clinical point of view, a consistent decreased response to influenza vaccine is observed compared to healthy younger adults

# *Clinical trial design key points*

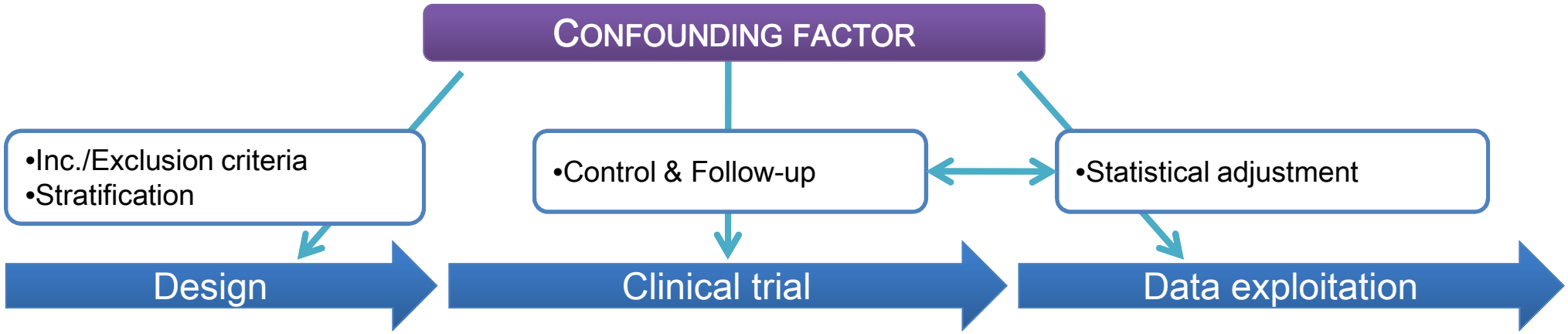
**CLINICAL TRIAL**

- Biomarkers / Endpoints
- Population
- **Confounding factors**
- Others

- Many factors can influence the clinical outcomes

⇨ Identify these factors is a cornerstone in the limitation of methodological biaises

# *Clinical trial design key points*




- **Experts review + literature review**

- **Examples for immunity claims:**
  - Physical activity greatly influences vaccination response
  - Ageing people usually take drugs that can interfere with vaccine response (blood thinners, corticosteroids etc)

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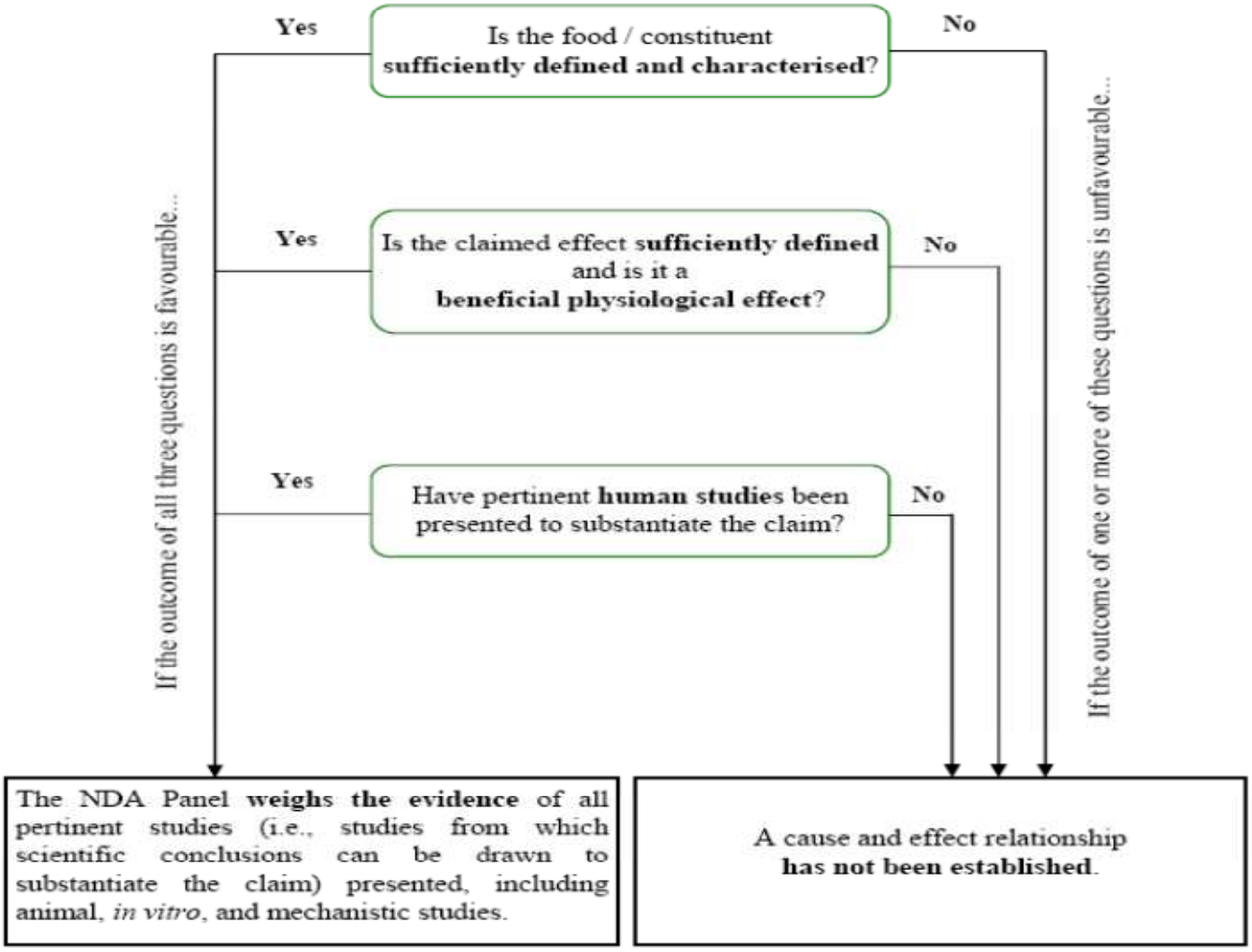
# EFSA Health claim evaluation tree




From Briefing document forArticle13 and 14 health claims evaluations , EFSA Journal 2010

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# *Main content of the dossier*

- Food/constituent for which a health claim is made
- Relationship between the food/constituent and the claimed effect
- Proposal for the wording of the health claim for which autorisation is sought
- Specific conditions of use
  - Target population
  - Quantity of the food/constituent required
- Food/constituent characteristics
  - Manufacturing process
  - Stability information
- Bioavailability data
- Body of pertinent scientific data identified
- Summary of pertinent scientific data

# *Case study : Water-soluble tomato concentrate (WSTC I and II) and platelet aggregation*

- Scientific substantiation of a health claim related to water-soluble tomato concentrate (WSTC I and II) and platelet aggregation pursuant to Article 13(5) of Regulation (EC) No 1924/20061
- The claim proposed by the applicant was worded as follows: 'Helps to maintain a healthy blood flow and benefits circulation'.
- The Panel concludes that a cause and effect relationship has been established between the consumption of water-soluble tomato concentrate and the reduction in platelet aggregation in humans. WSTC I and II and reduction of platelet aggregation
- The Panel could not have reached this conclusion without considering the studies claimed by the applicant as proprietary.
- The following wording reflects the scientific evidence: "helps maintain normal platelet aggregation".
- In order to achieve the claimed effect, 3 g WSTC I or 150 mg WSTC II in up to 250 mL of either fruit juices, flavoured drinks or yogurt drinks (unless heavily pasteurised) should be consumed daily. The target population is adults between 35 and 70 years of age.

*The EFSA Journal (2009) 1101,*

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# *Case study - (WSTC I and II) and platelet aggregation : product characterization*

- The WSTCs are standardized on the total quantity of 37 “bioactive” constituents identified and quantified using RP-HPLC-MS which have been shown to inhibit platelet aggregation in vitro to different degrees.

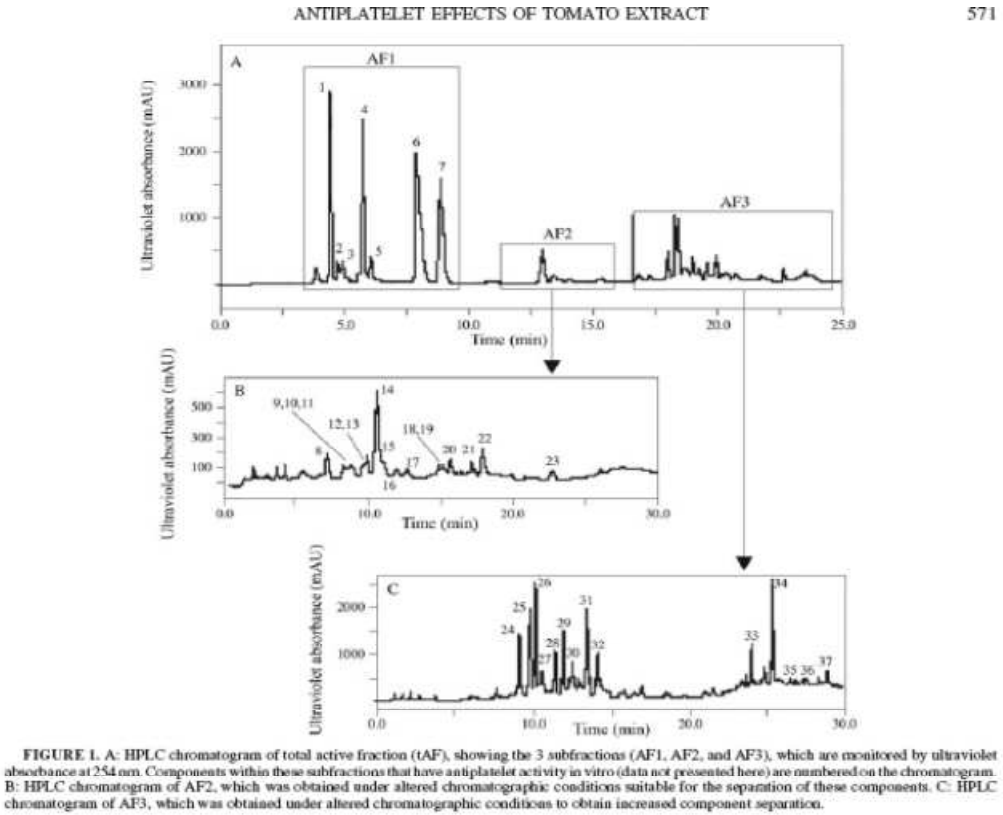


FIGURE 1. A: HPLC chromatogram of total active fraction (tAF), showing the 3 subfractions (AF1, AF2, and AF3), which are monitored by ultraviolet absorbance at 254 nm. Components within these subfractions that have antiplatelet activity in vitro (data not presented here) are numbered on the chromatogram. B: HPLC chromatogram of AF2, which was obtained under altered chromatographic conditions suitable for the separation of these components. C: HPLC chromatogram of AF3, which was obtained under altered chromatographic conditions to obtain increased component separation.

*Am J Clin Nutr 2006;84:570 –9*

- A number of physico-chemical characteristics have been assessed during stability testing, including breakdown products, pH, browning index, microbial status, ascorbate content, freeamino-acids, free uronic acids, free glucose and fructose, Amadori products, Maillard products.

*The EFSA Journal (2009) 1101,*

# *Case study - (WSTC I and II) and platelet aggregation : Relevance of the claimed effect to human health*

- The claimed effect is **"reduction in platelet aggregation"**. The **target population is healthy adults between 35 and 70 years of age.**

- The applicant has performed three well-described literature **searches to provide a rationale for the health benefits of reducing platelet aggregation in humans**. Platelet hyperactivity and hypercoagulability states are more commonly observed in subjects presenting cardiovascular (CV) risk factors (e.g., smokers, hypercholesterolaemic subjects, obese, diabetic) and have been shown to play a role in the development of atherosclerosis and its complications.

- The **development of different anti-platelet therapies has been a target for the prevention and treatment of cardiovascular disease .**

- The applicant argues **that healthy subjects at very low risk of CV disease (i.e, without risk factors) normally have non-activated circulating platelets, and that decreasing platelet aggregation in subjects with constitutive platelet activation would contribute to "normalise" or "restore" a "normal" platelet function**, which may be relevant in the context of delaying atherosclerosis progression and cardiovascular complications.

- The Panel **considers that maintaining normal platelet aggregation is beneficial to human** health.

*The EFSA Journal (2009) 1101,*

# *Case study - (WSTC I and II) and platelet aggregation : Scientific substantiation of the claimed effect*

- The applicant performed a literature search through three databases (Cochrane, Medline, Embase) using different combinations of keywords related to platelets and platelet activity (including haemostasis, thrombosis, cardiovascular disease) and tomato (or tomato extract/product) for retrieving controlled intervention studies in humans. The search strategy is clearly defined.

- The substantiation of the claimed effect is based on eight human studies (seven claimed as proprietary and conducted with WSTC) and seven (three claimed as proprietary) non human studies.

- In the seven human intervention studies claimed as proprietary, the effects of WSTC on platelet aggregation ex vivo was investigated in carefully selected male and female subjects between 35 and 70 years of age. The Panel considers that both the selection of subjects and the method used to assess platelet aggregation were appropriate for such studies.

*The EFSA Journal (2009) 1101,*

## *Conclusions*

- A tailor-made and step-by-step approach needs to be set-up to address the critical points regarding the substantiation of health claim EFSA in order to avoid the main pitfalls

*"One health claim = One R&D strategy for One EFSA dossier"*

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# NATURALPHA -*Today*

- Creation in 2001, based in Lille, France
- A Multidisciplinary Team
  - Physicians, Engineers, Research scientists, Nutritionists ,Dietitians
- A complete portfolio of services adapted to the changing environment
  - Consulting - Scientific & regulatory consulting and intelligence services
  - Laboratories – Preclinical validation, *in vitro* & *vivo* studies
  - Clinical Trials – Conception, conduction and management of clinical trials

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# Thank you for your attention

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