



Approval of probiotics in the EU – strategic choices, regulatory processes & key hurdles

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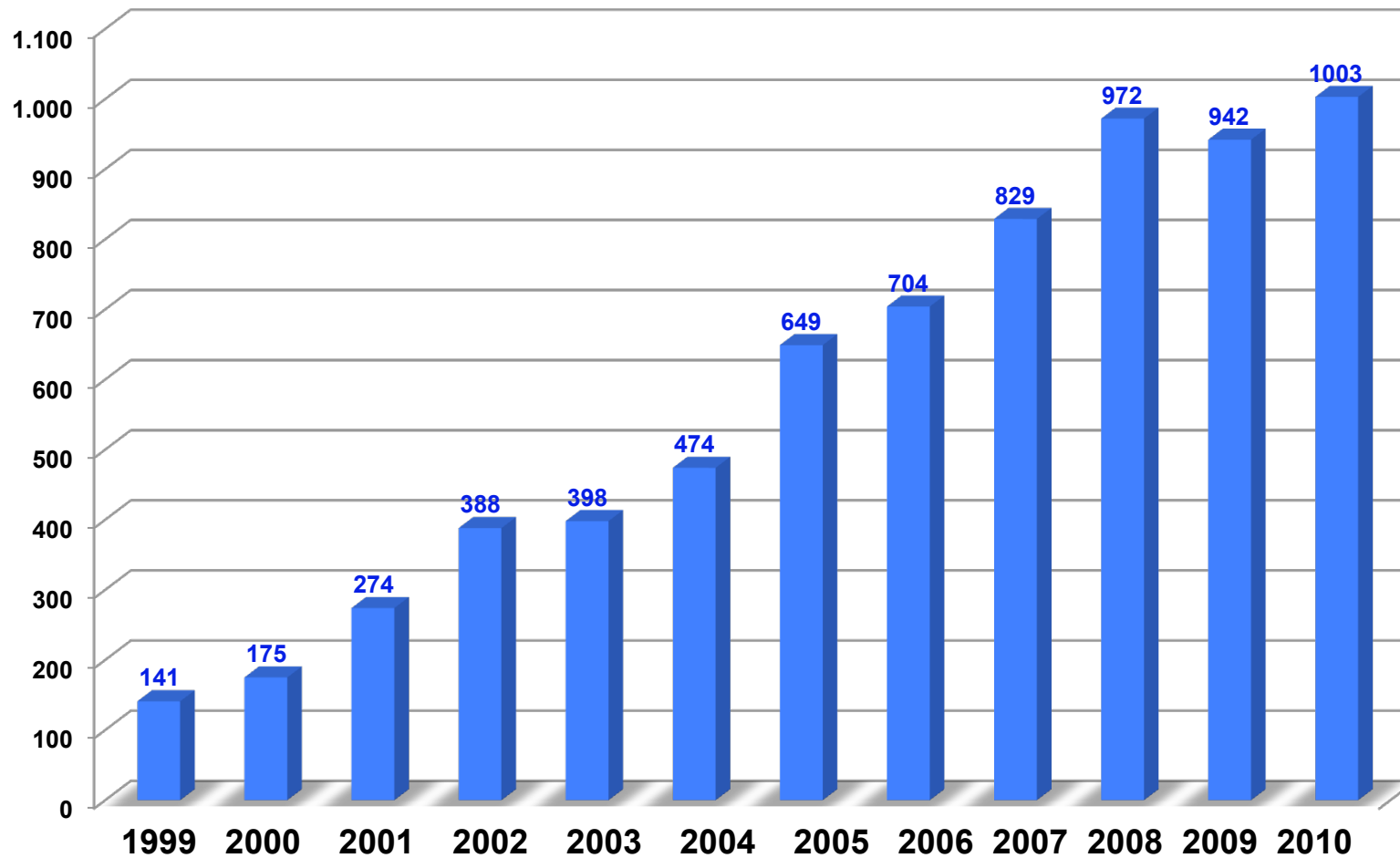
Dr Elinor McCartney
Pen & Tec[®] CONSULTING



- Introduction - current legal status of food probiotics in the EU
- FBOs (Food Business Operators) & food chain safety
- Probiotics, foods & food supplements – EU legal definitions
- Regulatory requirements – the strategic audit & gap analysis
- When is a probiotic considered a novel food?
- Novel Foods Regulation (Reg. 258/1997)
- What claims can I make about my probiotic?
- Nutrition & Health Claims Regulation (Reg. 1924/2006)
- EFSA NDA (Nutrition, Dietetic Products, Allergies) Guidance
- Current creative marketing strategies
- What about GMM probiotics? (Reg. 1829/2003)
- When is a probiotic dossier required?

Introduction:

Probiotic publications \approx 7,000 (Medline, 1999-2010)



Introduction: Current legal status of EU food probiotics



- “**GRANDFATHERING**”: Most food probiotic strains (≈260) are in transition (Reg. 1924/2006, Article 13.1 = GAS: Generally Accepted Science)
- “**TESTING THE SYSTEM**”: A few probiotic strains are attempting (& withdrawing) from Reg. 1924/2006 Article 13.5 (new/proprietary data) &/or Article 14 (children/health claims)
- “**SAFETY FIRST**”: A few probiotic strains may be subject to the novel foods regulation (Reg. 258/987)

Food business operators (FBOs) & food hygiene



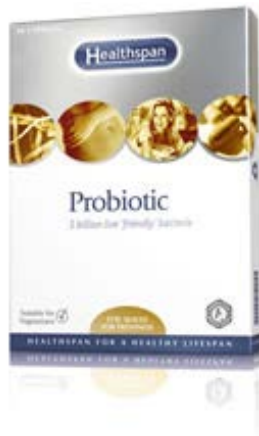
- **General requirements of EU food hygiene regulation:**
 - ✓ EU FBOs are responsible for EU food safety
 - ✓ Registration of EU FBOs with EU competent authorities
 - ✓ HACCP-based QC
 - ✓ Traceability & recall
 - ✓ Professional, competent, trained staff
 - ✓ Formal complaints procedure, etc.
- **Specific HACCP considerations for probiotic strains:**
 - ✓ **Toxins & virulence factors?**
 - ✓ **Antibiotic production & transfer of resistance?**

EU legal definitions: “Probiotic” – an implied health benefit!



Definition: Probiotics are:

‘live micro-organisms which when administered in adequate amounts confer a health benefit on the host’ (WHO 2002)



EU legal definitions: probiotics as foods & food supplements



- **Probiotics as foods** – examples are yogurts, dairy drinks, fermented fish, meats & vegetables, cheeses, etc.
- **Probiotics as food supplements** – examples are tablets, pills, powders, capsules, liquid concentrates in vials, softgels, etc

The strategic audit & gap analysis

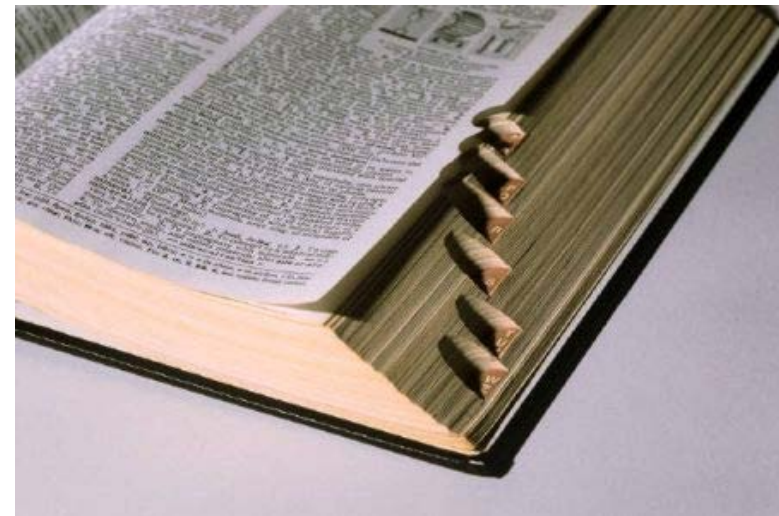


- **Strategic audit:**
 - ✓ What are the commercial aims for this probiotic?
 - ✓ Which EU regulations apply?
 - ✓ How do we comply?
 - ✓ How long will it take & how much will it cost?
 - ✓ Who, when, where, why, what if?
- **Gap analysis:**
 - ✓ Which existing data are OK?
 - ✓ What do we still need & where can we generate it?
 - ✓ Cost, time, reiteration?
 - ✓ Do we need an EU dossier?

When is a probiotic a novel food?



Novel Food Definition: Food/food ingredient that does not have a *significant history* of human consumption within the European Union prior to 15th May 1997



If in doubt check it out - with EU/Member State/s



IDF 2002: Inventory of micro-organisms with a documented history of use in food.



Novel foods regulation: a pre-marketing safety assessment



Regulation (EC) N° 258/97 concerning novel foods and novel food ingredients (states safety rules for authorisation of novel food/ingredients)

Commission Recommendation 97/618/EC (recommends information necessary to support an application to fulfil the safety assessment)

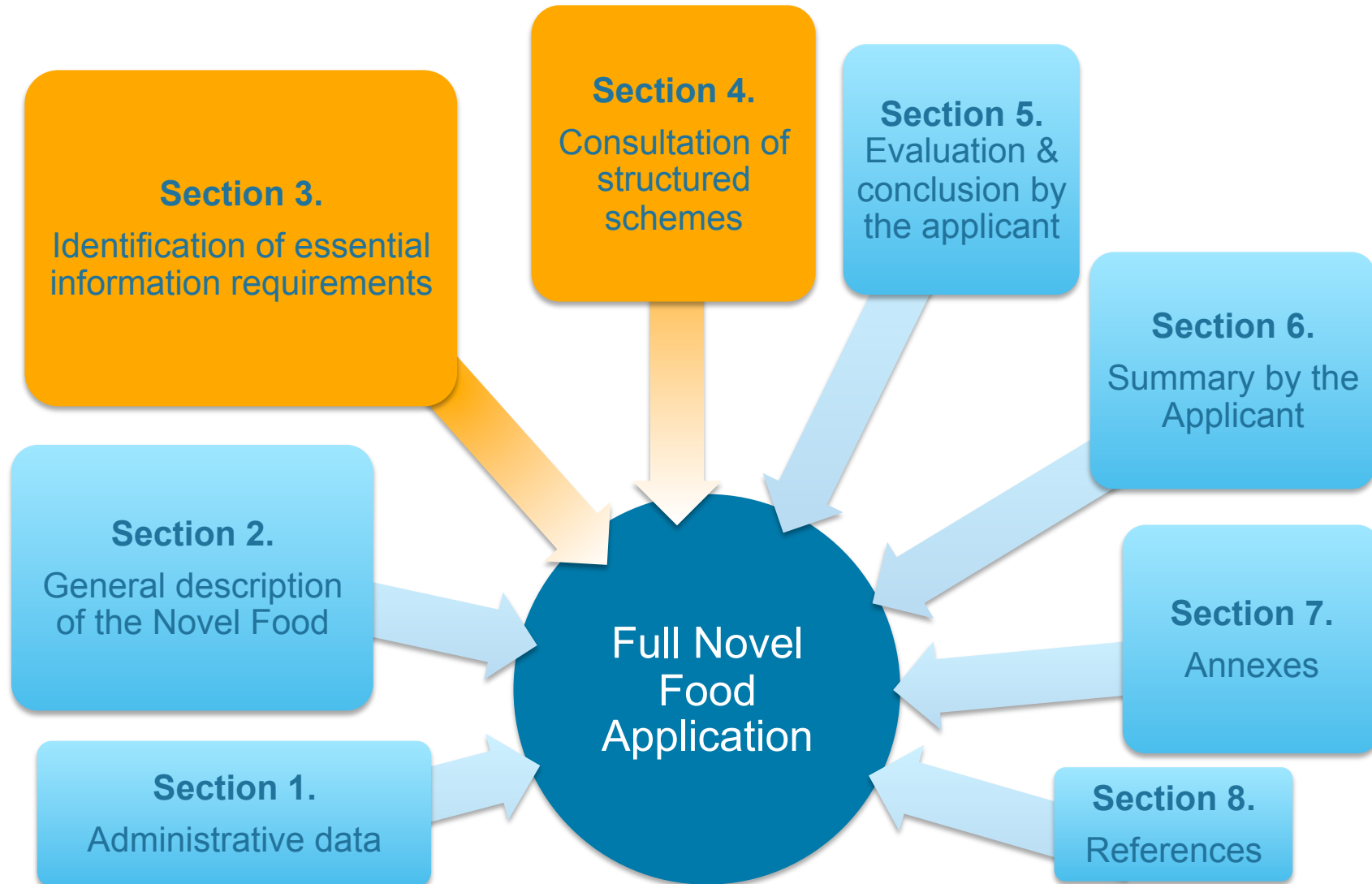


4 novel food categories



- Food/food ingredient with a new or intentionally modified primary molecular structure
- **Food/food ingredient consisting of or isolated from micro-organisms, fungi or algae**
- Food/food ingredient consisting or isolated from plants and food ingredients isolated from animals, except for foods and food ingredients obtained by traditional propagating or breeding practices and having a history of safe use
- Food/food ingredient to which a production process not currently used has been applied, where that process gives rise to significant changes in the composition or structure or the NF/NI which affect their nutritional value, metabolism or level of undesirable substances

Novel food application dossier



Novel food application for a probiotic



The scientific *classification* of the NF is established using Regulation 258/97:

Table II

Index to structured schemes to be followed for each class of NF

Structured scheme	Class of NF												
	1.1	1.2	2.1	2.2	3	4	5	6	7	8	9	10	
I. Specification of the NF	x	x	x	x									
II. Effect of the production process applied to the NF	x	x	x	x									
III. History of the organism used as the source of the NF	x	x	x	x									
IV. Effect of the genetic modification on the properties of the host organism													
V. Genetic stability of the GMO													
VI. Specificity of expression of novel genetic material													
VII. Transfer of genetic material from GM microorganisms					x	x	x	x	x	x	x		
VIII. Ability to survive in and colonize the human gut										x	x		
IX. Anticipated intake/extent of use of the NF	x	x	x	x	x	x	x	x	x	x	x	x	x
X. Information from previous human exposure to the NF or its source	x		x		x		x		x				x
XI. Nutritional information on the NF	x	x	x	x	x	x	x	x	x	x	x	x	x
XII. Microbiological information on the NF	x	x	x	x	x	x	x	x	x	x	x	x	x
XIII. Toxicological information on the NF	x	x	x	x	x	x	x	x	x	x	x	x	x



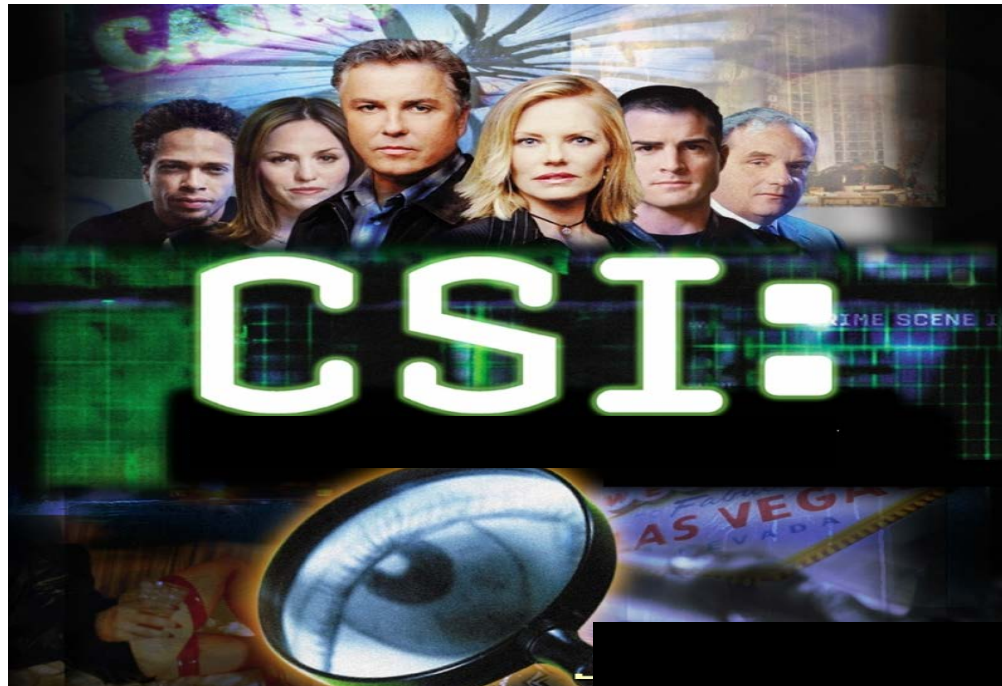
I. Specification of the novel probiotic strain



C *Characterised fully (genetic typing)*

S *Safe (no toxins, virulence, antibiotic production or mobile resistance)*

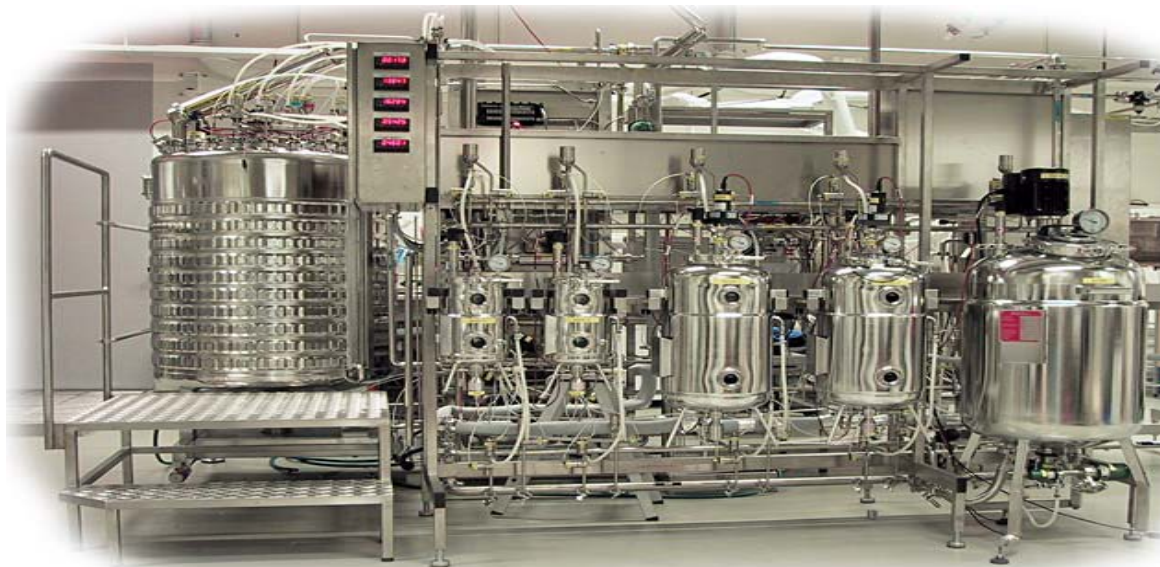
I *dentifiable (International Code of Nomenclature & strain deposit)*



II. Effect of the production process applied to the novel probiotic strain



- ✦ Production process
- ✦ Quality control



III. History of the novel probiotic strain



- ✧ Where, when first isolated?
- ✧ Is it a GMM? (!)
- ✧ Is it fully characterised (CSI)?
- ✧ Strain deposit details?
- ✧ Other uses & applications?

IV-VIII. GMMs as novel foods?



Table II

Index to structured schemes to be followed for each class of NF

Structured scheme		Class of NF							
		1.1	1.2	2.1	2.2	3.1	3.2	4.1	4.2
I.	Specification of the NF	x	x	x	x	x	x	x	x
II.	Effect of the production process applied to the NF	x	x	x	x	x	x	x	x
III.	History of the organism used as the source of the NF	x	x	x	x	x	x	x	x
IV.	Effect of the genetic modification on the properties of the host organism					x	x	x	x
V.	Genetic stability of the GMO					x	x	x	x
VI.	Specificity of expression of novel genetic material					x	x	x	x
VII.	Transfer of genetic material from GM microorganisms					x	x	x	x
VIII.	Ability to survive in and colonize the human gut								
IX.	Anticipated intake/extent of use of the NF	x	x	x	x	x	x	x	x
X.	Information from previous human exposure to the NF or its source	x		x		x		x	
XI.	Nutritional information on the NF	x	x	x	x	x	x	x	x
XII.	Microbiological information on the NF	x	x	x	x	x	x	x	x
XIII.	Toxicological information on the NF	x	x	x	x	x	x	x	x

✦ To date, no GMM probiotic dossiers in EU

IX. Anticipated intake/extent of use



- ✧ CFUs per day/per consumer?
- ✧ Use as food supplement?
- ✧ Use as food ingredient?
- ✧ Replace other foods, significant nutritional effects?
- ✧ Intake for “at risk” groups (infants/elderly)?
- ✧ Safety margin for consumers?

X. Information from previous human exposure (EU)

- ✦ Previous EU use in food supplement
- ✦ Proposed **new** use in sports drinks
- ✦ (Previous human exposure outside EU?)

Table II

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I.	Specification of the NF	x	x	x	x	x	x	x	x
II.	Effect of the production process applied to the NF	x	x	x	x	x	x	x	x
III.	History of the organism used as the source of the NF	x	x	x	x	x	x	x	x
IV.	Effect of the genetic modification on the properties of the host organism					x	x	x	x
V.	Genetic stability of the GMO					x	x	x	x
VI.	Specificity of expression of novel genetic material					x	x	x	x
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XI.	Nutritional information on the NF	x	x	x	x	x	x	x	x
XII.	Microbiological information on the NF	x	x	x	x	x	x	x	x
XIII.	Toxicological information on the NF	x	x	x	x	x	x	x	x

XI. Nutritional information on the novel probiotic



✧ Probably not relevant for probiotics used in food supplements

BUT

✧ May be relevant for new probiotics used in dairy & other foods

✧ Does novel probiotic replace other foods?

✧ Does novel probiotic affect bioavailability of nutrients?

✧ Does novel probiotics have adverse physiological effects?

XII. Microbiological information



- ✦ Are there any metabolites of adverse public health significance? (e.g. toxins & virulence factors, antibiotics)
- ✦ Adverse effects of production process? (→ show genetic stability of novel probiotic strain over time)
- ✦ Include final product specifications: undesirable microbial contaminants (**especially enteropathogens**), microbial quality, aflatoxins, heavy metals, etc.

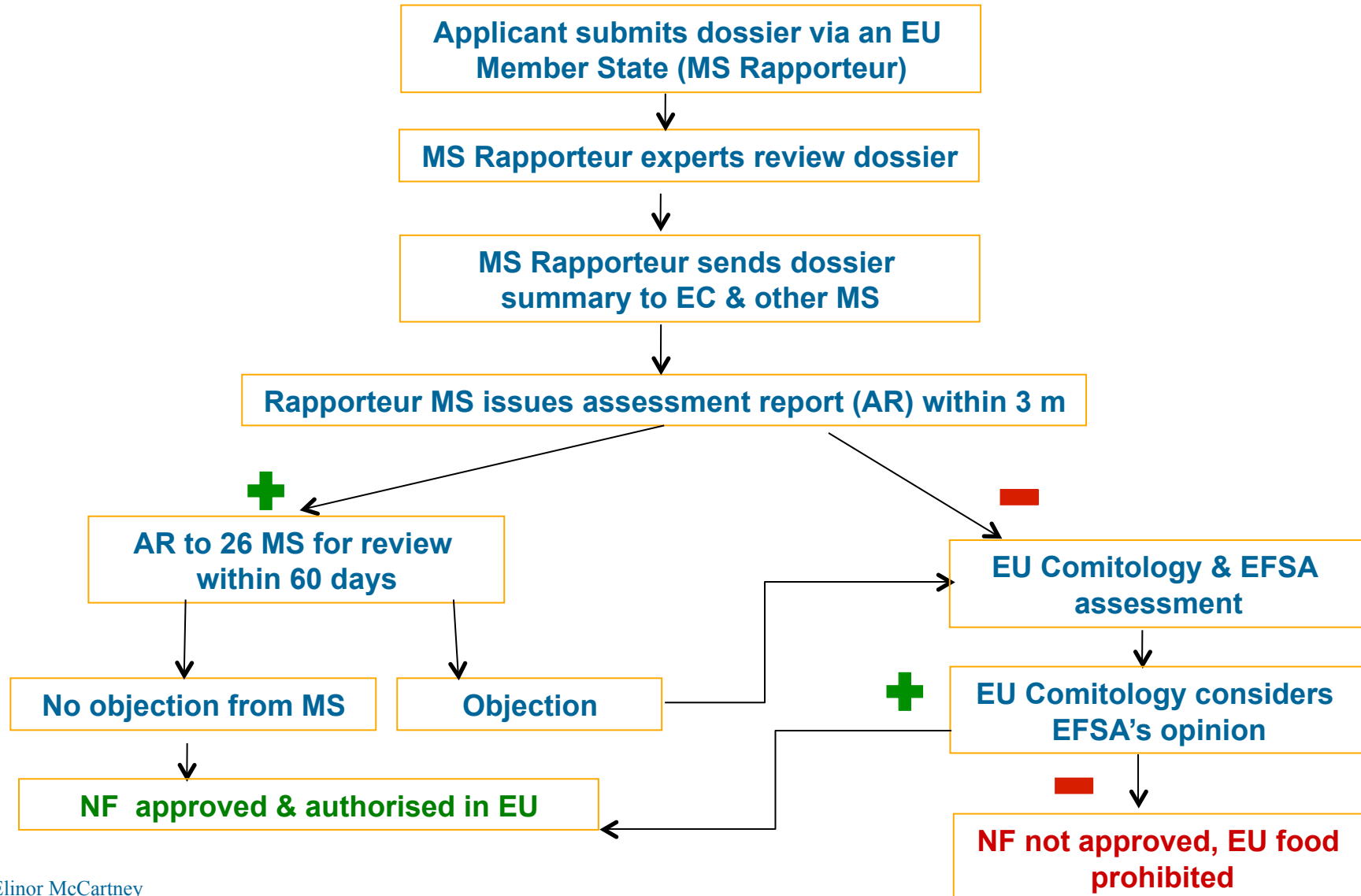


XIII. Toxicological information



- ✦ Toxicity studies *in vivo*, *in vitro* including mutagenicity studies, ~~reproduction & teratogenicity~~ studies
- ✦ QPS strains – *in vitro* studies (antibiotic production / transferable antibiotic resistance) No *in vivo* studies.
- ✦ Non-QPS strains – *in vitro* studies (toxins, virulence factors, antibiotic production & antibiotic resistance) & classic GLP/OECD studies:
 - ✦ 90-day rat study
 - ✦ 3-pack genotoxicity studies
- ✦ **Studies on potential ALLERGENICITY**

Novel probiotic dossier – EU evaluation



Key points on novel probiotic SAFETY



- ✦ No antibiotic production or transferable resistance
- ✦ Absence of toxins & virulence factors
- ✦ Strain MUST BE:
 - ✦ *Characterised (genetic typing)*
 - ✦ *SAFE (in vitro & in vivo safety studies)*
 - ✦ *Identified (ICN, strain deposit)*
- ✦ Allergenicity very important!
- ✦ EFSA take a strain-specific approach!



- What claims can I make about my probiotic?
 - ✓ Claims to scientists/health “professionals” OK
 - ✓ “Grandfathering” claims to consumers OK
 - Future claims to consumers – regulated



✓ **Approved**

or

✗ **Prohibited**

Probiotics and nutrition & health claims



- To date, EFSA has rejected ≈ 300 probiotic claims (Article 13.1)
- Current “resubmission” of fully-characterised strains - low success probability
- Article 13.5 (new/proprietary) - 6 new probiotic dossiers
- Article 14 (health/children) - 8 new probiotic dossiers
- EFSA (2011-2012) guidance documents:
 - ✓ **General & administrative guidance**
 - ✓ **Guidance on scientific requirements for claims on gut & immune function**
 - ⌘ Draft guidance on claims for a) bones, joints & oral health; b) antioxidants, oxidative damage & cardiovascular health; c) appetite ratings, weight management, & blood glucose
 - ⌘ Pending guidance on d) neurological & psychological functions; e) physical performance

Nutrition claims



Nutrition Claim – any claim which states, suggests or implies that a food has particular beneficial nutritional properties due to:

a. the energy it

1. provides
2. provides at a reduced or increased rate
3. or does not provide

b. the nutrients or ***other substances*** it

1. contains
2. contains in reduced or increased proportions
3. or does not contain

Health Claims



- **Health claim** - any claim that states, suggests or implies that a relationship exists between a food category, a food or one of its constituents and health, e.g. “functional/physiological” effects
- **Reduction of disease risk claim** - any health claim that states, suggests or implies that the consumption of a food category, a food or one of its constituents significantly reduces a risk factor in the development of a human disease

“PROBIOTIC” in consumer communications

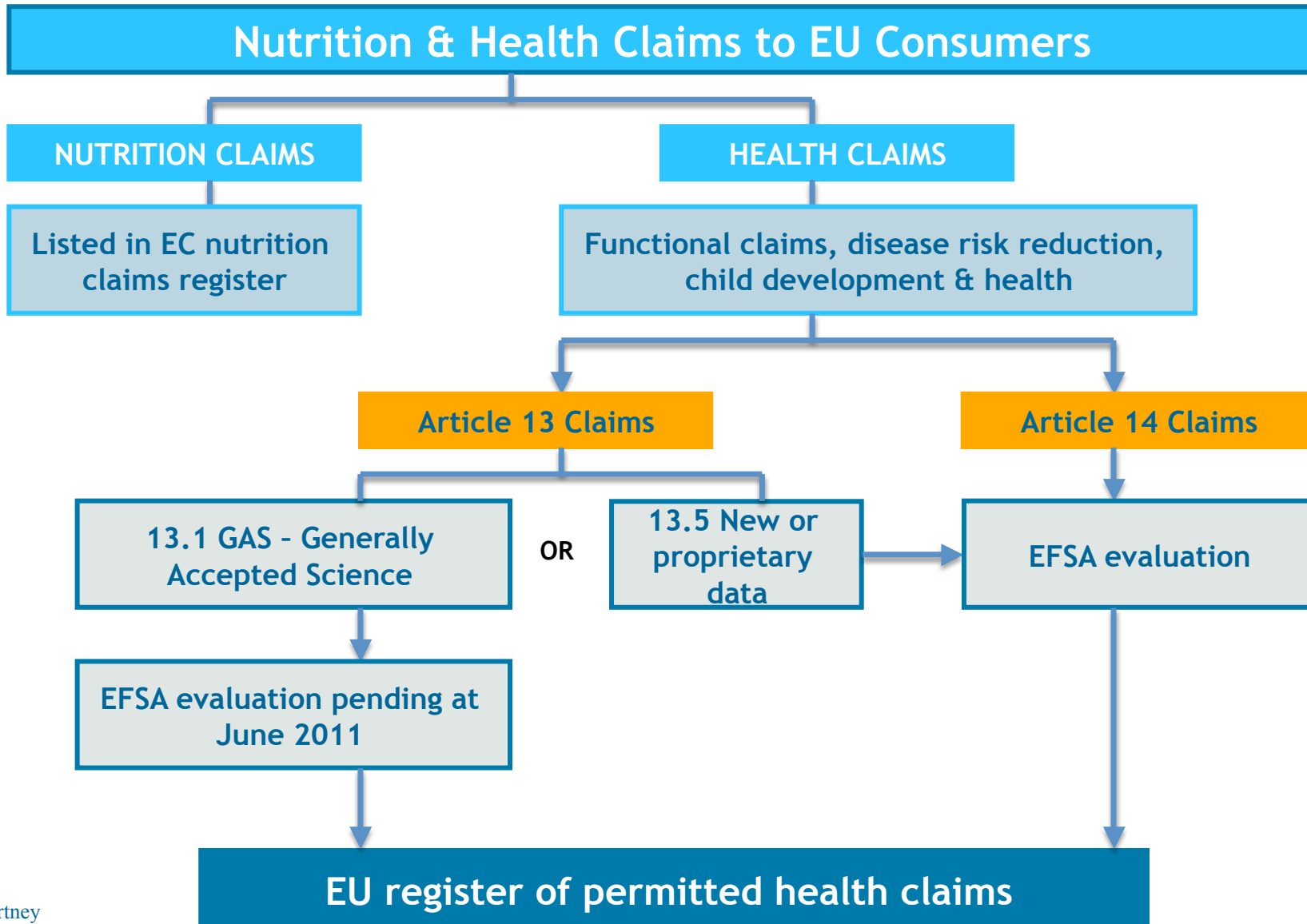


Health claims must *not*.....

- Be false, ambiguous or misleading
- Give rise to doubt about the safety and/or the nutritional adequacy of other foods
- Encourage or condone excess consumption of a food
- State suggest or imply that a balanced and varied diet cannot provide appropriate quantities of nutrients in general
- Refer to changes in bodily functions which could give rise to or exploit fear in the consumer, either textually or through pictorial, graphic or symbolic representation
- **“PROBIOTIC” implies a health benefit, hence may only be used when such a health benefit is established (EC dixit)**



Pathways to EU permitted food claims



Health Claims Articles 13 & 14



- Article 13.1: Claims based on 'generic' generally accepted scientific evidence (GAS) – “grandfathered” claims – e.g. role of probiotic in growth, development & bodily functions, (BUT time is running out!)
- Article 13.5: Claims based on new or emerging scientific evidence or proprietary data \ Article 18 procedure (except claims on children's development & health \ Articles 15, 16, 17 & 19)
- Article 14: Reduction of disease risk claims & claims referring to children's development and health \ Articles 15, 16, 17 & 19
- Importance of strategic audit at early stage of dossier project! What can be proven to EFSA's satisfaction?
- What claim wording is supported by the data?

Nutrition/Health claims dossier toolkit



Regulation (EC) N° 1924/2006
nutrition & health claims made on food

+

EFSA guidance documents
2011-2012

+

Consol. Reg. (EC) N° 353/2008

+

Future EFSA guidance/stakeholder
meetings/ Q&A's

=

Nutrition/Health
Claims dossier
“toolkit”

Data audit – what EFSA wants



- Did the efficacy studies use the probiotic strain/s or probiotic food in question?
- Have human studies used appropriate outcome measure/s **of the claimed effect?** (e.g. “gut health” ❌ vs. “intestinal transit time” ✓)
- Do the human studies reflect conditions of use? (e.g. **food intake & dose – CFU/day!**)
- What is the target group? Were studies performed in the target group? Can we extrapolate the data from study groups to other target groups?
- Which other studies are pertinent to the claim?

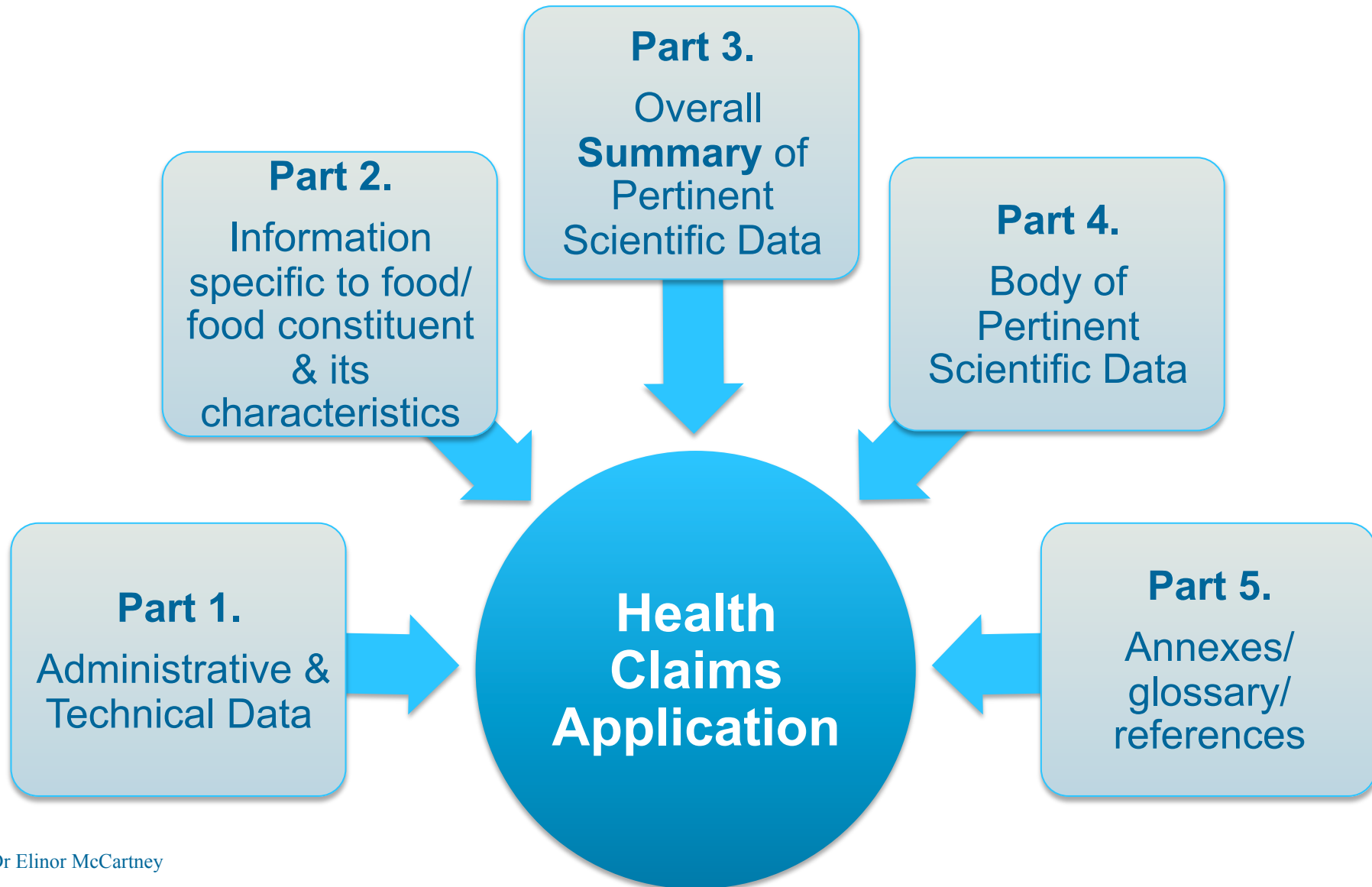
Procedure for nutrition/health claims dossiers



- Dossier sent to national competent authority (Member State, MS)
- MS acknowledges receipt within 14 days
- MS sends dossier to EFSA
- For **Article 14** (= diseases risk reduction +/- kids), **EFSA validates & copies** dossier to MS/EC & **publishes the dossier summary** (Art 15 route)
- For **Article 13.5** submissions (= new +/- proprietary data), the **MS** validates dossier, then forwards to other MSs & EC. (**No public summary?**)
- EFSA issues opinion 5 months after Clock 0 (valid dossier), excluding clock stops (+ at least 2 months for Art 14; + 1 month for Art 13.5)
- EC Comitology & approval/prohibition follow – several months

Nutrition & health claims dossier structure

Article 13.5 & 14 claims



EFSA consider dossier strengths/weaknesses



- Is the food/constituent sufficiently characterised (probiotic strain identity - CSI!)?
- Are the supporting studies carried out with the food/constituent that is subject of the claimed effect (strain-specific efficacy!)?
- Is supporting rationale available to explain how studies in animals or *in vitro* support the claimed effect in humans?
- Are the conditions under which the food/constituent administered in the human studies representative for the proposed conditions of use for the claim (e.g. intake/ consumption pattern – probiotic dose – CFU/day!)?
- Wording of claim OK – supported by the data?

Health claim approval process



- Applicant submits to MS competent authority.
- MS competent authority forwards to EFSA.
- EFSA review & issue an opinion.
- EU Commission & MS discuss & vote (Comitology/ QMV).
- Approval (or prohibition!) of claim & addition to the community register.



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Reasons for probiotic claim rejections



- Insufficient strain characterisation.
- Intestinal flora is not clearly defined.
- Claimed effect not clearly defined.
- Cause & effect relationship not established between the consumption of the probiotic & a beneficial physiological effect.
- Flaws in human intervention studies conducted.
- No human studies used to support the claim(s).

Current EU probiotic marketing strategies



- Focus on health “professionals”
- Maximising marketing expenditure during transitional phase (“imprinting”)
- “Association” techniques (e.g. exploiting R&D liaisons, branding & use of non-scientific strain names)
- Reformulating to take advantage of EFSA nutritional claims (e.g. Vitamin E & immunity)
- Innovative B-to-B & web/internet marketing

What about GMM probiotics?



- There are no GMM probiotics approved in the EU
- Any GMM probiotic requires a pre-marketing safety evaluation (Reg 1829/2003, EFSA GMO)
- Is the EU ready for GMM probiotics?

When is an EU probiotic dossier required?

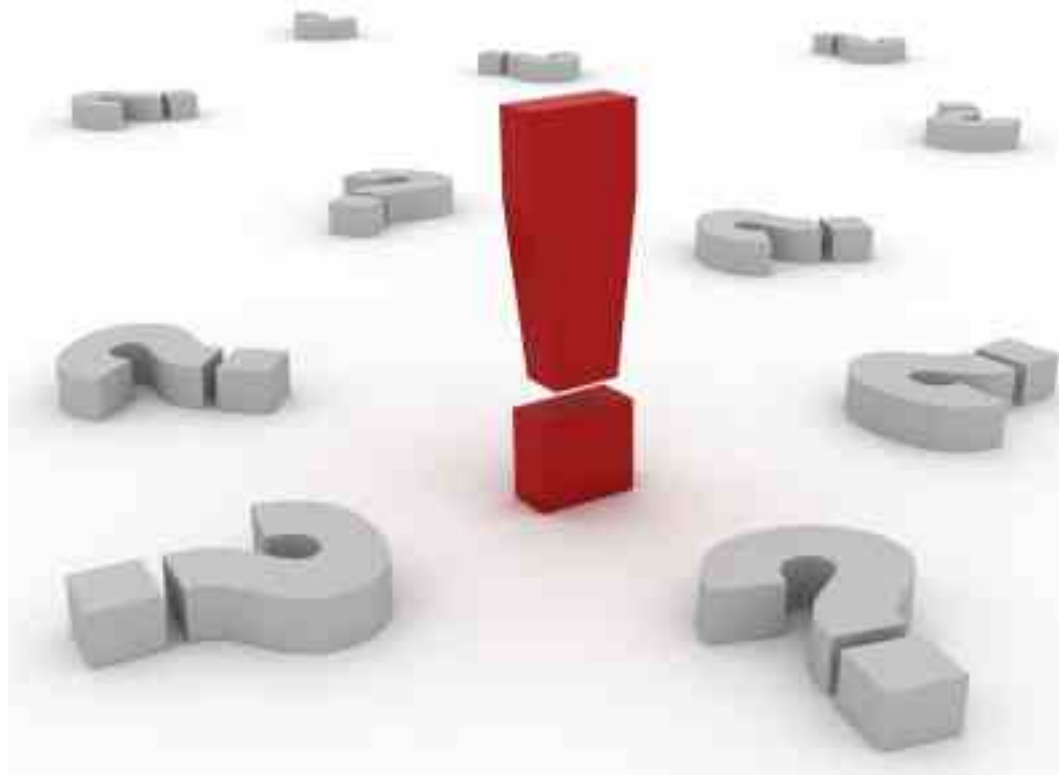


- GMM probiotic strains – EU GMM safety dossier (via EFSA GMO)
- Novel probiotic strains – EU novel foods safety dossier (via MS/EU +/- EFSA NDA)
- New use of probiotic strains – EU novel foods safety dossier (via MS/EU +/- EFSA NDA)
- Nutrition & health claims **to consumers** – EU efficacy dossier (via EFSA NDA))

Any questions?



I am happy to answer any questions



Many thanks for your attention



Dr Elinor McCartney
Technical Director
Pen & Tec Consulting

Passeig del Roser 135

Mirasol, Sant Cugat del Vallès

08195 Barcelona, Spain

E-mail: elinor@pentec-consulting.eu

Tel +34 93 675 80 15

Cell +34 699 053 898