pharmabiotic
research institute




BIOPOLIS
Tailor-made Biotechnology

Key regulatory issues in the development of pharmabiotics in Europe

Valencia, November 5th 2015

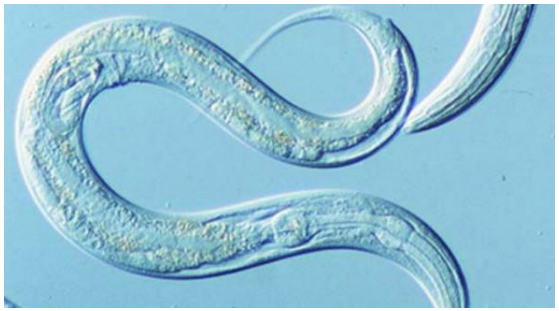
Biopolis is active in functional evaluation and infant nutrition as a developer of probiotics & oligosaccharides

Probiotics

- Full capabilities from screening to manufacturing
- Functionalities
  - Celiac disease
  - Gut inflammation
  - Metabolic syndrome
  - Rotavirus infection

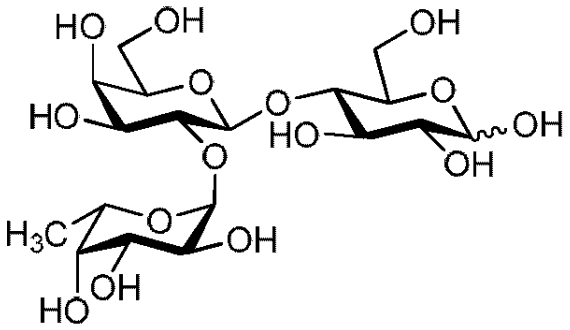
Evaluation

- Discovery & evaluation of functional ingredients, probiotics and APIs
- Proprietary models and panels of Biopolis using *C. elegans* and murine models
  - Inflammation
  - Oxidative stress
  - Fat metabolism



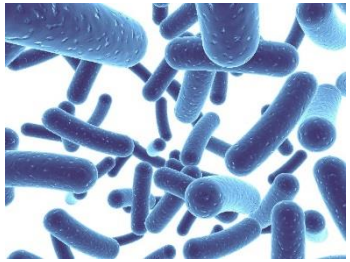
Functional ingredients

- R&D services for food & pharma industries
- Extensive expertise with human milk oligosaccharides for infant nutrition



Claims for microbial strains are (currently) only possible in the pathway of pharmaceuticals

Functional microbial strain



Food pathway
(probiotics)

Drug pathway
(pharmabiotics)

efsa
European Food Safety Authority

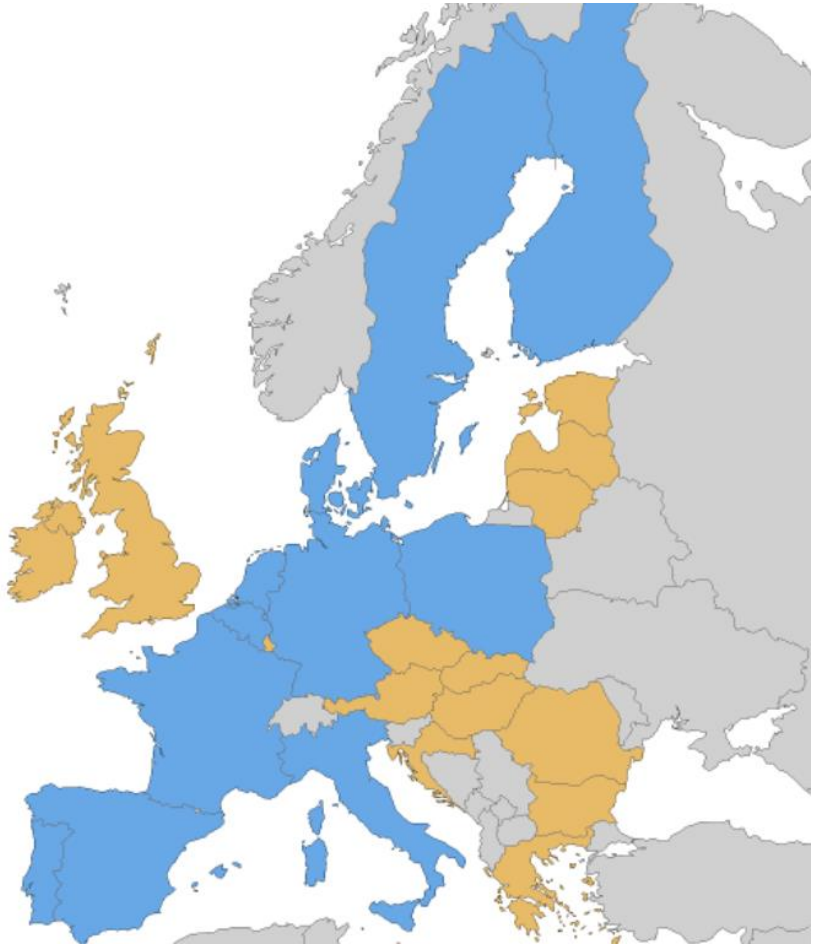
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- Limited to QPS species
- Health claims at most (none so far)

- No QPS limitation
- Disease claims suitable (need to prove)
- Developing field, regulation required

There is an enormous lack of harmonization in Europe

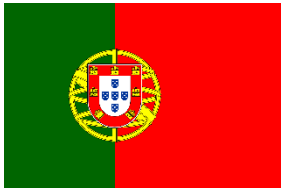
Regulatory status of *S. boulardii* in the EU



EU countries in which *S. boulardii* is a drug

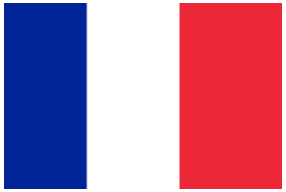
EU countries in which *S. boulardii* is not a drug

Non-EU countries



infarmed
Autoridade Nacional do Medicamento e Produtos de Saúde I.P.

"Os bacilos lácticos e as leveduras não têm provas convincentes da sua eficácia terapêutica."

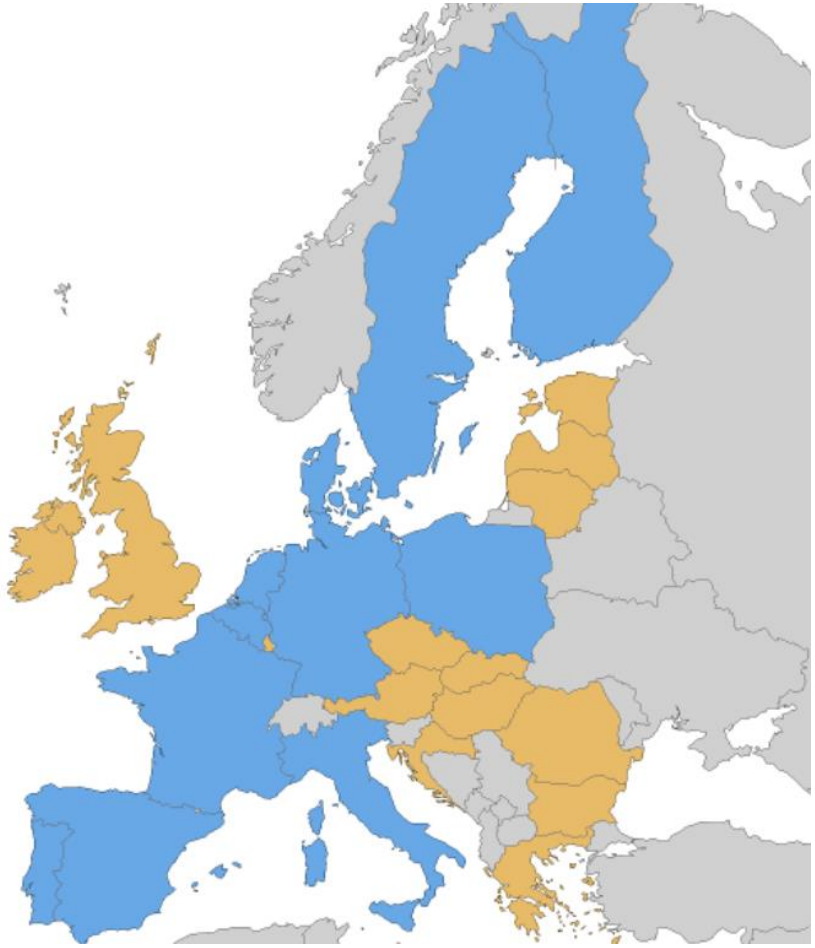


ansm
Agence nationale de sécurité du médicament et des produits de santé

"L'efficace clinique de ce médicament dans le traitement des diarrhées n'a pas été documentée par des essais contrôlés."

There is an enormous lack of harmonization in Europe

Regulatory status of *S. boulardii* in the EU



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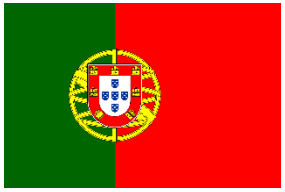
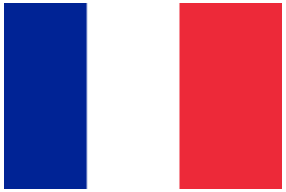


infarmed
Autoridade Nacional do Medicamento e Produtos de Saúde I.P.

"Lactic acid bacilli and yeasts do not have convincing proof of therapeutic efficacy."



ansm
Agence nationale de sécurité du médicament et des produits de santé

"The clinical efficacy of this medicine for the treatment of diarrhea has not been documented by controlled studies."

Microorganisms are regarded as Rx and even non-substitutable biologics in some countries

Número de Registro:	311001-9	Medicamento:	ULTRA LEVURA CAPSULAS
Laboratorio titular:	BIOCODEX	Estado del medicamento:	Autorizado 28/05/2004
Principios Activos:	SACCHAROMYCES BOULARDII	Medicamento no sustituible:	Biológicos
Clasificación ATC:	Nivel 3: A07F - MICROORGANISMOS ANTIDIARREICOS		
	Nivel 4: A07FA - Microorganismos antidiarreicos		
	Nivel 5: A07FA02 - Saccharomyces boulardii		

Número de Registro:	34702	Medicamento:	CASENFILUS POLVO
Laboratorio titular:	LABORATORIOS CASEN-FLEET, S.L.U.	Estado del medicamento:	Autorizado 01/10/1960
Principios Activos:	LACTOBACILLUS ACIDOPHILUS	Medicamento no sustituible:	Biológicos
Clasificación ATC:	Nivel 3: A07F - MICROORGANISMOS ANTIDIARREICOS		
	Nivel 4: A07FA - Microorganismos antidiarreicos		
	Nivel 5: A07FA01 - Ácido láctico, organismo productores de		

Prescription partly drug (Source: Finnish Medicines Agency-FIMEA, November 2015)

Prescription drug and subject to special pharmacovigilance as *Biotechnology Drug*
(Source: Swedish Medicines Agency, November 2015)

FDA guidance is mainly focused on CMC rather than safety or efficacy matters

U.S. Food and Drug Administration
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

GUIDANCE FOR INDUSTRY

Live Biotherapeutic Products

TABLE OF CONTENTS

I. INTRODUCTION 2
A. Purpose and Scope 2
B. Definitions 3
II. BACKGROUND 4
III. ADMINISTRATIVE AND REGULATORY PROCEDURES 5
A. Pre-IND Advice and Meetings 5
B. Address for Submission of INDs 6
C. Drug Master Files 6
IV. CHEMISTRY, MANUFACTURING, AND CONTROL (CMC) INFORMATION 6
A. Regulatory Considerations 6
B. Drug Substance 7
1. Description 7
2. Characterization 8
3. Manufacturer 9
4. Method of Manufacture 9
5. Drug Substance Specifications 12
C. Drug Product 13
1. Composition 13
2. Manufacture 13
3. Drug Product Specification 13
4. Stability 14
5. Placebo 14
6. Environmental Assessment 14
V. NON-CLINICAL INFORMATION 15
VI. CLINICAL INFORMATION 15
A. Previous Human Experience 15
B. Proposed Initial Studies 16
VII. REFERENCES 17

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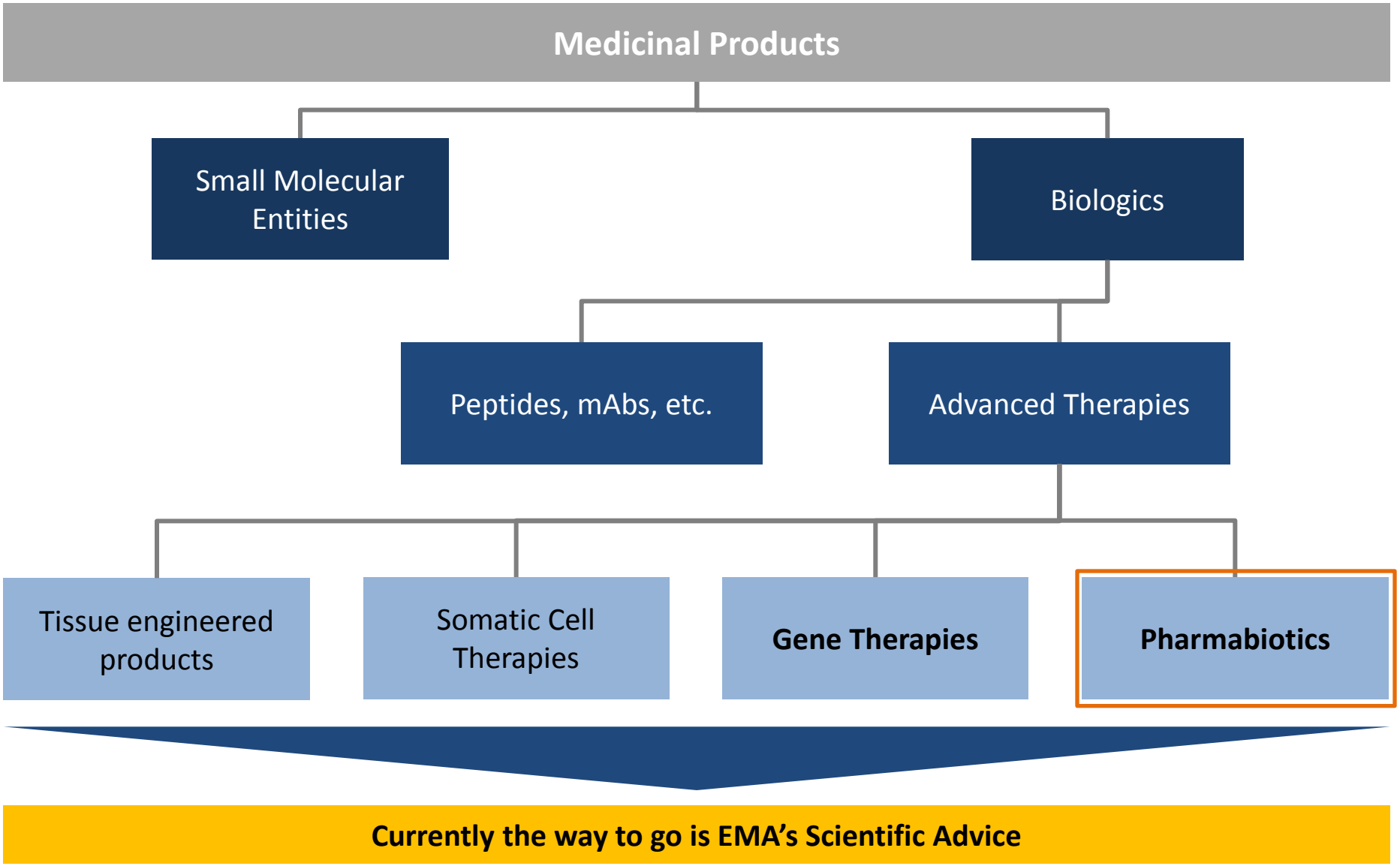
Five key regulatory issues for the development of pharmabiotics

1. Regulatory category
2. Safety
3. Efficacy - MoA
4. Efficacy - Potency
5. Efficacy – Clinical trial design & Biomarkers

Five key regulatory issues for the development of pharmabiotics

1 Regulatory category

Pharmabiotics may constitute a novel category within Advanced Therapy Medicinal Products



Five key regulatory issues for the development of pharmabiotics

BIOpolis

2 Safety

2 QPS species or approved food ingredients may not be exempt from Phase I - safety trials

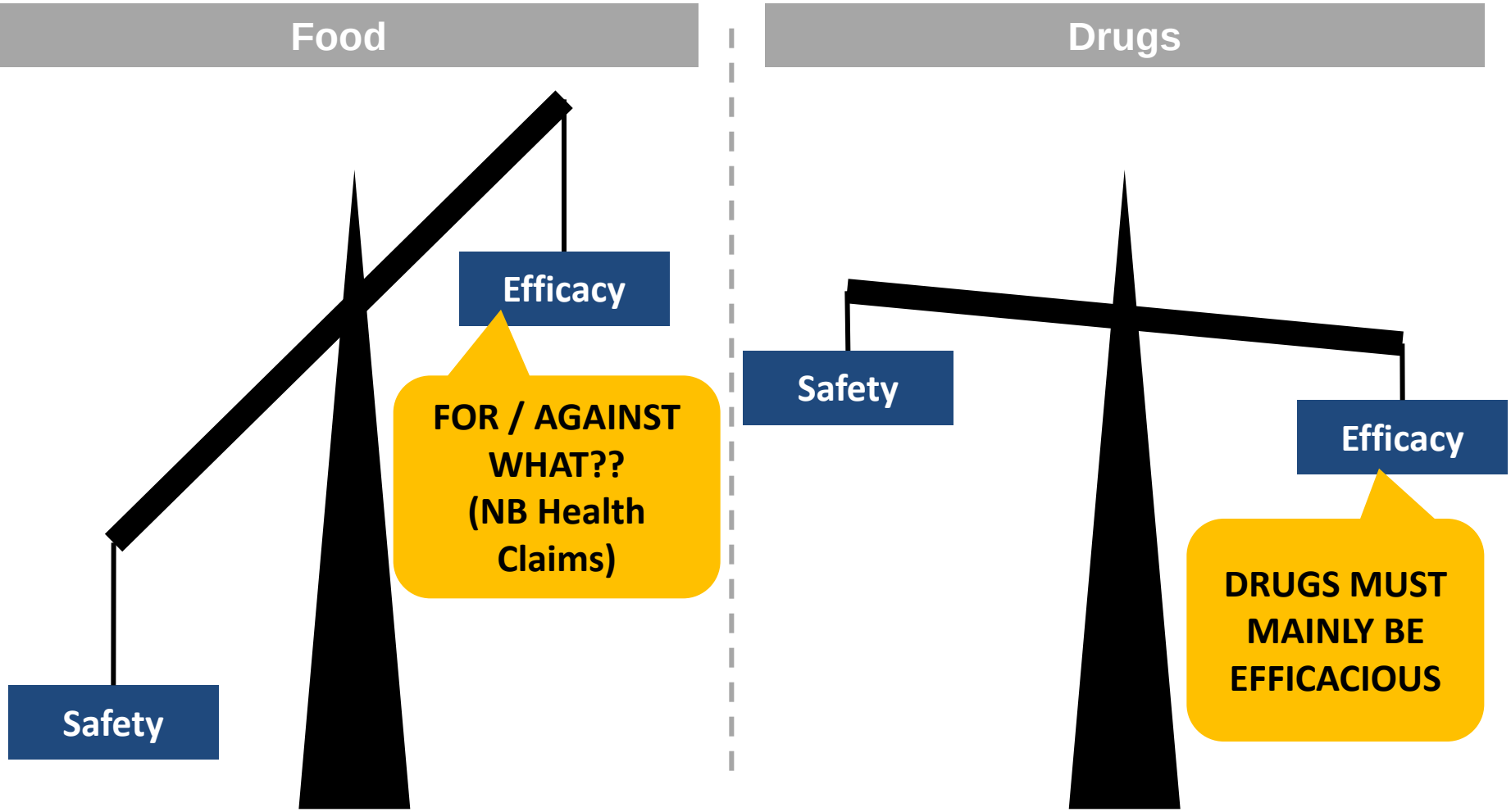
- There is debate around strains belonging to QPS species being systematically waived of safety testing, but authorities say that even foods with long history of use may be required Phase I – safety trials as drugs

> ***"Food and dietary supplement products that are intended for use as drugs are not exempt from IND requirements. Thus, if a clinical investigation is intended to evaluate the ability of a LBP to diagnose, cure, mitigate, treat or prevent a disease, an IND is required."***
>
> FDA Guidance for Industry

- Following every step of drug development will be advantageous:

a. Take into account that we may be working with severely-diseased population in drug development
b. QPS list would certainly be too narrow for pharmabiotics
c. Differentiating these developments from food programs
d. *Safety* means different things in pharmaceuticals and in food

Drugs have risk/benefit trade-off but food does not. The approach to safety must be different too.



Safety as drug is different to *food safety*

Five key regulatory issues for the development of pharmabiotics

3 Efficacy - MoA

4 Efficacy - Potency

5 Efficacy – Clinical trial design & Biomarkers

3 Elucidation of the ultimate MoA may not be required for pharmabiotics

- The level of complexity of the biology, the physiology and the ecology of pharmabiotics is much larger than the one of any other drug
- Developers are concerned about the requirements on mechanism of action (MoA) elucidation

> ***"If the Mechanism(s) of action(s) is known, you should submit data in the IND to support the mechanism(s) of action(s)."***
>
> FDA Guidance for Industry

- The situation is similar in biologics (and biosimilars), where the knowledge of the MoA is usually limited

> ***"The pharmaco-dynamic action correlated to the efficacy shall be demonstrated including* […] *mode of action, if possible"***
>
> Directive 2001/83/EC on medicinal products for human use

Limited knowledge of the ultimate MoA should not be an issue for pharmabiotics

4 Potency measures additional to CFUs will likely be required for pharmabiotics

- Traditionally potency has been measured as CFUs
- However, the amount of cells may not be the only way pharmabiotics work
- Additional indicators of potency may be required (production of metabolite, expression levels, metabolic activities…)
- Elucidation of the ultimate MoA may be important to support potency

> ***"Potency and/or biochemical or physicochemical measurements thought to predict potency. Generally […] colony-forming units (CFUs). Additional measures of product potency may be applicable, depending on the […] product […] and knowledge of the mechanism(s) of action."***
>
> FDA Guidance for Industry

> ***"Whenever possible, evidence that the selected potency assay correlates with activity or efficacy observed in clinical trials should be provided."***
>
> FDA Guidance for Industry

> ***"If you are able to identify a limited number of genes that may be potency-indicating, we recommend that you investigate the genetic stability of those genes."***
>
> FDA Guidance for Industry

5 Validated clinical endpoints are necessary due to the lack of definition of *eu/dysbiosis*

- Considerations when designing clinical trials:

Healthy vs. *Diseased*	Inclusion / exclusion criteria	Special considerations for population groups
Improvement, Worsening, Relapse	Study endpoints	Biomarkers (microbiota-related?)

- Microbiota-related measurements will likely not be accepted by authorities given the lack of definition of *health* vs. *disease*, *eubiosis* vs. *dysbiosis.*
  - *"Should microbiota be considered an organ not to be altered?"*
  - *"Should its alteration towards* health *be the objective?"*
- However, they may be used to support efficacy or MoA.
- Studies' final endpoints must be <u>clinical</u>. Ex. *Clostridium* strain for IBD:

Clinical endpoints

- Time to relapse / to recovery from surgery
- Rectoscopy / colonoscopy observations
- Pain indicators…

Surrogate & exploratory endpoints

- Inflammation markers: CRP, TNFα, IL-10
- Microbiota profile…

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