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

![Image of probiotics and oligosaccharides](image-url)
Claims for microbial strains are (currently) only possible in the pathway of pharmaceuticals

**Functional microbial strain**

- **Food pathway (probiotics)**
  - Limited to QPS species
  - Health claims at most (none so far)

- **Drug pathway (pharmabiotics)**
  - 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**

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

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

“*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

*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.

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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

Currently the way to go is EMA’s Scientific Advice
Five key regulatory issues for the development of pharmabiotics

2 Safety
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

Food
- Safety
- Efficacy

Drugs
- Safety
- Efficacy

FOR / AGAINST WHAT?? (NB Health Claims)

DRUGS MUST MAINLY BE EFFICACIOUS
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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
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
Validated clinical endpoints are necessary due to the lack of definition of eu/dysbiosis

- Considerations when designing clinical trials:
  - Healthy vs. Diseased
  - Improvement, Worsening, Relapse
  - Inclusion / exclusion criteria
  - Study endpoints
  - Special considerations for population groups
  - 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 clinical. 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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