Chapter 7
A Quantitative Key-Opinion-Leader Analysis of Innovation Barriers in Probiotic Research and Development: Valorisation and Improving the Tech Transfer Cycle

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7.1. Abstract

The field of probiotics has great innovative potential, addressing several unmet medical needs. However, despite mounting evidence and opportunities in the field, relatively few strains are commercially available and probiotics are seldom in routine use in clinical practice. Innovation in the field of probiotics seems hampered. Using the barrier approach, this study identified the main barriers in the probiotic innovation process, as experienced by key-opinion-leaders (KOLs). These innovation barriers are visualised and their underlying causes revealed by means of qualitative root cause analysis. The root causes were placed in an academic-industrial valorisation cycle. Furthermore, a quantitative ranking of the barriers was used to demonstrate their relative importance. This study demonstrates that the probiotic research cycle is faulty due to specific barriers and bypasses, and that innovation is hampered in all domains of the valorisation cycle. Eleven main barriers were identified, with “difficulty in demonstrating clinical efficacy” being the most significant inhibiting factor. Other barriers could be classified as fundamental research barriers, clinical research barriers, financial barriers, regulatory barriers, collaboration barriers, marketing barriers and product barriers. Using this barrier approach, inhibiting factors are identified which allows subsequent action to be taken to re-establish the natural cycle of innovation.
7.2. Introduction

Due to advances in the NIH Human Microbiome Project, there is an increased understanding in how the microbiome affects human health, and in specific the association between dysbiosis and disease. Modulation of gut dysbiosis by probiotics seems promising. Probiotics are defined as ‘live microorganisms that, when administered in adequate amounts, confer a health benefit on the host’ (Hill et al., 2014). Currently, there is an increasing scientific as well as a commercial interest in probiotics. The word “probiotics” alone gave > 12,000 hits on PubMed (including MEDLINE), of which 766 are published in this year (July 2015). As for the commercial interest, the global probiotic market is estimated at $15 billion dollar (Caselli et al., 2013), with an estimated annual growth of 7% (Foligné et al., 2013).

There are indications that probiotics can be beneficial in a wide range of clinical conditions as well as for maintaining health (Sanders et al., 2013). There is consensus that probiotics in general can enhance colonization resistance, produce acid and short-chain fatty acids, regulate the intestinal transit, normalize the perturbed microbiota, increase turnover of enterocytes and exclude pathogens by competition; whereas neurological, endocrine and immunological effects can be observed in specific strains (Hill et al., 2014). Specific probiotic strains already demonstrated a strong positive outcome in literature for certain clinical conditions (Floch, 2014). This concerns diarrhoea such as antibiotic-associated diarrhoea (AAD) and infectious diarrhoea, inflammatory bowel disease (IBD; prevention and remission of pouchitis and maintenance of ulcerative colitis; UC) and prevention and treatment of allergy (Floch 2014). When focusing on specific target populations, evidence for probiotics in infants is strongest for necrotizing enterocolitis (NEC). In children, evidence is best substantiated for acute infectious diarrhoea, AAD and lactose malabsorption. The same holds true for AAD and malabsorption in adults and elderly, in addition to pouchitis (Sanders et al., 2013). Other potential targets for probiotics, which have shown effect to some degree are colic, irritable bowel syndrome (IBS) symptoms, common infectious diseases, atopic dermatitis (AD), growth parameters of malnourished children, UC, travellers’ diarrhoea and vaginal infections (Sanders et al., 2014).

Innovation is essential in a highly complex and dynamic environment such as the health industry (Begun et al., 2003). Innovation can be defined as “the intentional introduction and application within a role, group, or organisation, of ideas, processes, products or procedures, new to the relevant unit of adoption, designed to significantly benefit the individual, the group, or wider society” (West, 1990; Länsisalmi et al., 2006). Especially in the probiotic industry, there is great innovative potential, since probiotics may address several unmet medical needs for which alternative therapies are lacking. For instance, a reduction in the duration of diarrhoea (by approximately one day; Guandalini, 2011) or the prevention of NEC in preterm low-birthweight infants can be achieved by probiotic administration (AlFaleh and Anabrees, 2014).

Despite piling evidence and opportunities in the field of probiotics, relatively few strains are commercially available and probiotics are seldom in routine use in clinical practice. The European Food Safety Authority
EFSA has rejected all health claims on the benefits of probiotic bacteria, even claims supported by solid scientific evidence (Guarner et al., 2011). In addition, the label “probiotics” by itself is no longer allowed by EFSA on products containing probiotic strains (Glanville et al., 2015). Whether these rejections are valid or not, innovation in the field of probiotics seems significantly hampered.

One way to approach innovation deficiencies is by focusing on the main barriers in the innovation process. By understanding the nature, origin and relative importance of innovation barriers, deeper insight is gained in the impact of the barrier on the innovation process. The understanding of barriers can aid in the process of overcoming them and thereby encourage an environment that supports innovation (Weenen et al., 2013). Using the barrier approach, inhibiting factors and their effects can be identified and subsequently action can be taken to eliminate them, re-establishing the natural cycle of innovation (Hadjimanolis, 1999; Dehzad et al., 2014).

Barriers are factors that negatively influence the innovation process, and prevent commercial utilization of the innovation (Weenen et al., 2013). A differentiation can be made between external and internal barriers. External barriers include e.g. lack of fundamental knowledge, finance, customer demands and regulation. Internal barriers include for instance a lack of internal funds, technical expertise and human related barriers (Hadjumanolis, 1999). As external and internal barriers can be applicable cross-industry, both are taken into account in this study.

It is essential to identify the point of impact of barriers in the innovation process and to analyse their effects or consequences. The Valorization & Technology Transfer Cycle by Pronker (2013) provides a more holistic overview of the innovation process (Pronker, 2013). Adapted to this research, the Valorization Cycle is subdivided into four segments (Figure 7.1). The first segment is fundamental (curiosity-driven) research, where an idea is realized into a patent or publication through empirical evaluation. After realization of an idea, there is a transition into the clinical and business development segment. Successfully going through the steps of proof-of-concept, evaluation (clinical, legislature and quality) and industrial upscaling will lead to market introduction and customer feedback. In the final segment of society the unmet need articulation takes place which feeds back into research. All steps in the Valorization Cycle are important for the innovation process and barriers might act on one or more points in the Valorization Cycle (Pronker, 2013).

### 7.2.1. Research objective

To our best knowledge, there is no literature on innovation and potential barriers in the field of probiotics. This research aims to identify the main barriers, as experienced by KOLs in the probiotic innovation process, and visualize these innovation barriers and their underlying causes by means of qualitative root cause analysis.
Although the Valorization Cycle offers a clear guideline for linking unmet needs to the academic response repertoire and into prototyping for the market, further granularity is needed to plot individual barriers in such a way that defined actions and priorities become visible. For this reason we extended the Valorisation & Technology Transfer Cycle (Figure 7.2) which was developed for vaccine R&D to be used in probiotic/microbiota R&D (Pronker, 2013). Furthermore, this study demonstrates the relative importance of these barriers by a quantitative ranking by key-opinion-leaders.
Figure 7.2. The Microbiota Valorization & Technology Transfer Cycle V1.0. Efficient transfer of knowledge is greatly facilitated when all domains are aware of specific actions that need to be taken in order to propagate the target compound in the (improvement) cycle. Please Note: actions under 3a & 3b fall in academic space and are essential in intellectual property (IP), valorisation, utilisation and societal dissemination paragraphs. Most notable R&D bias is found in: pilotitis i.e. develop products in academic setting not available for actual use; innovation paradox i.e. “more research is needed” leading to new ideas without progressing through entire cycle; lack of unmet need and or societal agenda as explicit in lack of demand driven supply chain.
7.3. Methods

The methodology of this study was based on the barrier analysis in the field of medical nutrition by Weenen et al. and health applications by Dehzad et al. (Weenen et al., 2013; Dehzad et al., 2014). Data was generated in three different stages. First, KOLs were interviewed to gain insights in the current innovation barriers in the probiotic market and their respective underlying causes. In the second stage, a root-cause-analysis was performed to determine the main barriers and their underlying causes. In the final stage, KOLs were asked to rank the barriers according to their relevance and importance.

7.3.1. Semi-structured interviews

For the exploration of the current innovation barriers in the field of probiotics, semi-structured interviews were conducted with KOLs. An individual with extensive knowledge in the field of probiotics (research, market or clinical development) was considered a “Key-opinion-leader”. A selection of 25 KOLs from different perspectives (industry, academia and regulation), were informed by mail and subsequently invited to participate in this research. A semi-structured interview design was used to allow new ideas to emerge (Verschuren et al., 2010). Open questions were posed concerning potential innovation barriers and the underlying causes. In total 16 participants agreed to participate in this research. The total number of interviews was based on saturation of innovation barriers. Interviews were analysed using theme coding (Weenen et al., 2013). Main barriers were identified and used for the quantitative ranking in the questionnaire.

7.3.2. Root cause analysis

To enhance understanding of the causes and visualize associations between arguments, a root cause analysis tree was developed. Based on the study by Weenen et al. (2013) and adapted to fit the field of probiotics, this process allowed a structured framework to identify the main inhibiting factors in the innovation process based on the data from the semi-structured interviews.

7.3.3. Questionnaire

An online questionnaire was developed to rank the main innovation barriers for probiotics using the online web survey tool Survey Monkey®. This anonymous online questionnaire was pilot tested and distributed among KOLs. The questionnaire consisted of three open questions and two questions where KOLs were
asked to rank innovation barriers. A total of 127 KOLs were identified and selected to participate in this research (practicing medical doctors; MDs, researchers, dieticians, regulators, consultants and business developers). Additional KOLs were invited to participate in this research at scientific symposia about probiotics (e.g. at the International Scientific Association for Prebiotics and Probiotics). The snowball technique was used to find more participants, every KOL was asked to suggest other KOLs that could be contacted for this study. KOLs that did not respond to the initial invitation received a follow up letter after 7 days to increase the response rate. In addition to quantitative barrier ranking, KOLs were asked to provide additional innovation barriers and their perception on how these inhibiting factors hampered the innovation process. The following formula was used to calculate the relative weight of an innovation barrier:

\[
WR_B = \frac{\sum((n_{r1} \times 3) + (n_{r2} \times 2) + (n_{r3} \times 1)) \times 100}{\sum((n_{r1} \times 3) + (n_{r2} \times 2) + (n_{r3} \times 1))_{HRB}}
\]

WR, weighted ranking; B, barrier; HRB, highest ranked barrier; n, number of times; R1/2/3, rank1/2/3.

### 7.4. Results

A total of 16 KOLs agreed to participate in the interviews. Saturation was achieved after 12 interviews; a total of 37 barriers in the probiotic innovation process were identified in the initial analysis (see Figure 7.3). The barriers could be categorized into fundamental research barriers, clinical research barriers, financial barriers, regulatory barriers, collaboration barriers, marketing barriers and product barriers. Of the 83 participants that initially responded to the invitation, only 48 KOLs fully completed the online questionnaire. The majority of the respondents aged between 40 and 55 yrs (54.2%) followed by 24 to 40 yrs (29.2%) and 55 yrs and up (16.7%). The positions that the respondents fulfilled were academic (43.8%), practicing MD (31.3%), consultant (10.4%), industry representative (10.4%) and dieticians (4.2%). Respondents were from 12 different countries.
Root-cause-analysis synthesized 37 barriers into 11 main barriers, which were subsequently ranked by KOLs. Difficulty of demonstrating clinical efficacy proved to be the most important barrier (100, weighted relevance), followed by competition with probiotics with no evidence-base (55) and regulatory approval (43). Other barriers that negatively influenced innovation concerned competition between the food and pharma industry (35), high costs of clinical trials and INDs (35), poor investment in probiotic research & development (R&D; 31) and a lack of scientific knowledge of probiotics (31). The remaining innovation barriers did not exceed a weighted relevance above 25, indicating a relatively low importance (Table 7.1).

When placing the barriers from table 7.1 as mentioned by the KOLs in a flow chart together with the underlying causes as shown in Figure 7.4, a more detailed picture of the barriers & causes in the innovation process emerges (Figure 7.5).
Table 7.1. Innovation barriers for the field of probiotics, from quantitative KOL survey, ranked according to their relative importance. IND, Investigational new drug.

<table>
<thead>
<tr>
<th>Rank</th>
<th>Innovation barrier</th>
<th>Weighted relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Difficulty demonstrating efficacy</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>Competition with marketed probiotics with no evidence base</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>Regulatory approval</td>
<td>43</td>
</tr>
<tr>
<td>4</td>
<td>Competition between food and pharma industry</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>High costs clinical trials/IND application</td>
<td>35</td>
</tr>
<tr>
<td>6</td>
<td>Poor investment probiotic research &amp; development</td>
<td>31</td>
</tr>
<tr>
<td>7</td>
<td>Lack of scientific knowledge probiotics</td>
<td>31</td>
</tr>
<tr>
<td>8</td>
<td>Poor collaboration between industries (food &amp; pharma) and academia</td>
<td>24</td>
</tr>
<tr>
<td>9</td>
<td>Lack of professional research &amp; development</td>
<td>17</td>
</tr>
<tr>
<td>10</td>
<td>Negative perceptions of probiotics</td>
<td>15</td>
</tr>
<tr>
<td>11</td>
<td>Small return on investment</td>
<td>0</td>
</tr>
</tbody>
</table>

7.4.1. Scientific discourse

In recent years the beneficial potential of probiotics in the human host has become more evident due to new sequencing techniques and functional genomics. Nevertheless, fundamental knowledge of the human microbiome, and the place of probiotics in this intestinal ecosystem, is still in its infancy. There is a lack of knowledge on the mechanism of action (MoA) of probiotics, the strain characterization of how different probiotic strains are affected by lifecycle (e.g. different genes are induced in stationary cells compared to logarithmic cells; van Baarlen et al., 2009), the effect of industrial processing and matrices on gene expression (e.g. commercially available Lactobacillus rhamnosus GG lacking potentially important surface proteins) and on how the environment, e.g. GIT-transit, affects gene expression and function.

In addition, there is a lack of biomarkers to measure and define a healthy microbiota and effective markers for measuring certain clinical conditions. The main underlying cause for these barriers is that there is insufficient fundamental research due to a lack of public funds and insufficient industry sponsorship.
Figure 7.4. Root cause analysis of innovation barriers in the fields of probiotics. CT, clinical trial; MoA, mechanism-of-action; IND, investigational new drug; RA, regulatory authorities; R&D, research & development; ROI, return-on-investment.
There is a poor collaboration between food and pharma industries, and between both industries and academia. This is among other reasons due to a lack of interest in probiotics by pharma, because of the relatively small return-on-investment (ROI). As probiotics move into the medicinal claims, it leads to competition between food and pharma industry, which hinders collaboration. There is also poor cooperation between industry and academia, due to intellectual property rights and differences in objectives. In addition, to meet the standards for high-quality studies, chemistry, manufacturing and controls (CMC) practices are required.
However, most manufacturers are disinterested or unwilling to provide for the necessary requirements, thereby making it impossible for investigators to adequately study the probiotic products (Hibberd and Davidson, 2008).

### 7.4.2. Development discourse

Demonstrating clinical efficacy proved to be the most influential barrier for the field of probiotic innovation. This can be attributed to clinical trial difficulties which are inherent to evaluating probiotics. One of these underlying factors is the subtle effects of probiotics. Almost all probiotics are transient passengers in the gastrointestinal tract (GIT), and their relative abundance in the gut, apart for the duodenum, remains very low ($10^9$ vs. $10^{14}$ colony forming units). In addition, as it concerns live organisms, their interaction with the GIT-environment remains difficult to predict. There is also a lack of biomarkers to demonstrate effectiveness and it is therefore still unclear how to demonstrate the effect of probiotics, especially in the healthy population. Demonstrating changing concentrations in blood proteins or immune cells has proven to be insufficient for most regulatory bodies to grant a claim (Katan, 2012). Another underlying factor is the poor translation from preclinical animal models to human clinical studies and an inability to generalize clinical trial (CT) outcomes. The latter can be subscribed to high interpersonal variability in microbiota, as well as to regional differences (Arumugam et al., 2011). The composition of the microbiota depends on several factors including age, genetics, environment, diet, disease condition and antibiotic use (Lozupone et al., 2012). This variability in the microbiota of individuals is an extremely difficult confounding factor for CTs, and potential positive outcomes of CTs in the developed world cannot easily be extrapolated to, for instance, developing countries.

As a result of these inherent CT difficulties that form a serious barrier to probiotic innovation, the inability to provide solid clinical evidence hinders probiotic products to get past the proof-of-concept step in the valorisation cycle. Demonstrating clinical efficacy is furthermore hindered by insufficient quality of clinical studies. Many studies are underpowered and the study populations and clinical indications heterogeneous, which make it difficult to draw conclusions. Furthermore, clinical studies are few, leading to limited knowledge regarding the optimal dose-response, regimen, duration of the treatment, window of opportunity and optimal matrix. According to the KOLs, this can be attributed to a lack of professional research & development (R&D) and poor investments in R&D in the food and food supplement industry (compared to for instance the pharma-industry). Currently, research efforts are fragmented and diluted. This poor investment in R&D can be subscribed to a lack of funds to support the extreme high costs of CTs and investigational new drug (IND) applications. The high risk of failure due to inherent clinical trial difficulties combined with the risk of unsuccessful clinical trials negating the sales of already commercially available probiotic products, inhibits industry to invest heavily in rigorous clinical studies. In addition, there is a relative small ROI compared to medicinal products, exclusivity is not always guaranteed and industry
is reluctant to invest in R&D when competitor probiotic products without any evidence substantiation are already marketed. Besides the financial inhibiting factors, food industry companies do not want food and food supplements to be associated with diseases. Consumers make a clear distinction between food supplements (e.g. probiotics) and drugs. In general, consumers do not see foods and dietary supplements such as probiotics as drugs, and therefore a part of the probiotic industry is not willing to focus on R&D for diseases.

Effects of probiotics are situated on too many levels; due to complexity of the question (many different mechanisms) and diversity of the population in terms of microbiota composition, nutrition and immune status, research efforts are diluted. Furthermore, there is an over-reliance on in vitro studies to demonstrate probiotic efficacy, despite a poor translation to humans.

The third most important barrier ranked by the KOLs is the difficulty in obtaining regulatory approval. Currently, the regulatory framework for probiotics is unclear. Based on their respective claim, probiotic products are marketed as foods, dietary supplements, medical foods, foods for special dietary use, or drugs (Hoffmann et al., 2013). For instance, probiotics aimed at maintaining health (foods and dietary supplements) are completely differently regulated than probiotics aiming to treat, mitigate or alleviate a disease (Sanders et al., 2013; Hill et al., 2014). The latter is considered as a drug and to substantiate its claim, the product should go through the time consuming and costly process of an IND application, including all the inherent difficulties that probiotics face in general. A health claim is defined as “any claim that states, suggests or implies that a relationship exists between a food category, a food or one of its components and health” (Flynn, 2012). A health claim can refer to three types of claims; a function claim, a claim on reduction of disease risk and claims for development and health of children (Flynn, 2012). A health claim is legally different from a medicinal claim. Despite the fact that foods and dietary supplements can have a curative capacity, due to the Western approach to medicine, no claims can be made regarding treatment, alleviation, mitigation or prevention of diseases. KOLs deemed these regulations outdated. Discrepancies between regulatory authorities across the globe furthermore make probiotics hard to regulate and provoke uncertainty and confusion (Arora et al., 2015). It is possible for probiotics to obtain a medicinal claim through an IND process; however, evaluation standards based on the pharma-principle are not suitable, as certain requirements are extra challenging due to the dynamic nature of probiotics. For instance, probiotic are live and dynamic organisms that degrade over time and react to their environment and vice versa. Additional barriers mentioned by KOLs are an unclear definition of probiotics and poor capacity of regulatory review panels to appreciate the available data.

Technical difficulties with industrial upscaling form another barrier in the process of probiotic product innovation. Probiotic properties in a laboratory setting can significantly differ from large-scale production due to differences in matrices, growth phases and genomic expression (Bove et al., 2013). In addition, technological difficulties in improving shelf-life remain a barrier for probiotic product innovation.
7.4.3. Market and society discourse

One of the major barriers for probiotic innovation is that probiotics can be made commercially available without any evidence-base or substantiated claim. Probiotic products can be marketed as foods or food supplement without a health claim, as long as they are considered safe (e.g. a generally recognised as safe (GRAS) designation or its European equivalent (QPS; Herody et al., 2010) qualified presumption of safety). Although a solid evidence-base is missing, in today’s society where self-management of health has become increasingly important, these products already return high revenues when sold as supplements (Bandura, 2005). This resulted in flooding of the market by so called ‘pirate probiotics’ and discourages companies to enhance the evidence-base for their products. The efficacy of these pirate probiotics is doubtful. Due to a lack of proper quality control, some of these products on the market have a lower viability than claimed on the label (Carr and Ibrahim, 2005). In addition, in some cases these products even contain no probiotics at all, or contain pathogenic strains. As the market is dominated by probiotic products which are marketed without a sufficient evidence-base, negative perceptions regarding probiotics emerge. Over-exaggerated claims, ineffective strains and the conflation of probiotics form the root cause of these negative perceptions. In a vicious cycle, the public notion that probiotics are ineffective leads to a lack of public interest in probiotic research and thus in the absence of public funding. Furthermore, lack of information in (general) press give probiotics a poor image. Insufficient information provided to primary care practitioners, and the erroneous notion that one strain could relieve a disease or pathology furthermore result in negative perceptions and low acceptance of probiotics among physicians.

7.5. Conclusion and Discussion

This study made evident that the Valorization cycle of probiotics is faulty by analysing the barriers to innovation in the field of probiotics. In addition, this study provides a ranked overview of the most important inhibiting factors in the probiotic industry as identified by KOLs and identifies which steps in the valorisation cycle are hampered. Seven different types of barriers were identified: fundamental research barriers, clinical research barriers, financial barriers, regulatory barriers, collaboration barriers, marketing barriers and product barriers. The most important barriers were the difficulty of demonstrating efficacy (i), competition with marketed probiotics without evidence base (ii) and the difficulty in obtaining regulatory approval (iii). The specific combination of innovation barriers leads to an arrest of innovation in this field and it is therefore essential for the probiotic industry to acknowledge these barriers and act accordingly to overcome them. Developing strategies for an innovative climate will not only stimulate industrial growth and commercial survival, additionally it will fulfil unmet medical needs.
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A causal factor for the faulty valorization cycle of probiotics is that in many cases probiotic strains are not selected based on their MoA or potential effects in specific clinical conditions, but rather on their superb growth properties. Lack in fundamental knowledge of probiotics as well as inherent clinical trial difficulties and poor study designs result in an innovation halt in the stage of clinical and business development. Due to insufficient investment in R&D and professional R&D, studies are heterogeneous and underpowered. This phenomenon is termed “pilotitis”, whereby the small and diffused projects do not support a sufficient evidence-base to obtain regulatory approval. Investigators do not seem to get past the proof-of-concept phase, and in most cases probiotic research will not go through rigorous evaluation in clinical trials. Strikingly, the number of meta-analyses compared to clinical trials is for some clinical indications out of proportion (e.g. ratio for NEC is 1:2 respectively; Pubmed, 2015). Since probiotic products can bypass the evaluation step in the clinical and business development stage, and directly penetrate the market as a food or dietary supplement without a claim, companies that put an effort in scientific research are negatively affected by competition ‘pirate’ probiotics. Bypassing a step that health innovation processes would naturally follow results in disintegration of the cycle and arrests probiotics in that stage of development (Pronker, 2013). In addition, it makes companies reluctant to invest in R&D if they already have sales, since negative study results can negate their turnover. Ineffective products and a lack of evidence-base, result in poor physician-acceptance and consumer confidence. This translates into no societal demand for probiotic research, which in turn, negatively influences progress in fundamental research in the microbiota and probiotics. Figure 7.6 illustrates this negative spiral of the current probiotic innovation cycle.

7.5.1. Overcoming the innovation barriers

As several key factors hamper the innovation cycle of probiotics, there is no easy strategy to overcome these barriers. Nevertheless, a cross-industry cooperative effort in combination with the regulatory authorities can create a progressive environment for probiotic innovation.

According to the KOLs, a promising strategy to restore the innovation cycle is to increase cooperation and communication between industry, academia and the regulatory authorities. This can take form in joint research projects of industry and academia and early inclusion of regulatory authorities in the product development. Unification of the several probiotic associations (e.g. IPA, ISAPP, EPA and YLFA) would make them more powerful and efficacious in representing probiotic interests. Increased communication towards health professionals and improved information dissemination to the general public on probiotics could restore the current negative perceptions. Whether the pharmaceutical industry should cooperate with the food industry, as it is often thought that the pharma industry has all the scientific and regulatory expertise, remains dubious. It has been shown in several cases that despite having ample experience with clinical trials, pharma lacks the necessary specific knowledge of the food industry. In addition, the food industry has proven to be equally capable of producing a science base for their product (Mellentin, 2007).
From the perspective of the pharma industry itself, there are however equally good reasons to not allocate funds to this kind of research since that the margins on these foods/food supplements are significantly lower compared pharmaceutical products (5% vs. 20%; Mellentin, 2007).

Another suggestion by KOLs to overcome these probiotic innovation barriers is to increase scientific research efforts. Not only should there be more fundamental research on the MoA of probiotics, but also more rigorous and serious, well-designed, (over)powered, multi-centre clinical trials to evaluate the efficacy of probiotics. To achieve this, sufficient funds should be allocated to research in probiotics, not only from industry, but also from public funding bodies. There is an important role for KOLs to disseminate clear information regarding results to regulatory authorities, MDs and the general population. For instance, after the failed PROPATRIA-trial, the notion that probiotics can be harmful still exists, regardless of demonstrated safety of probiotics, even in immune compromised individuals and preterm infants (van den Nieuwboer, 2014a, b). With this in mind it is important that research focuses on achievable outcomes, and that the exaggerated claims of probiotics are reduced (e.g. Probiotics for weight loss; Park and Bae, 2015).
On the other hand, regulatory bodies should relax somewhat in evaluation of dossiers. EFSA and FDA require robust mechanistic data; however, this is difficult as probiotics concern live organisms. Currently, the claims that EFSA rejected were based on insufficient quality of studies, in terms of weak study designs, execution and analysis. In addition, validity and interpretation of biomarkers of body function and disease risk were considered weak (Flynn, 2012). Regulatory bodies also consider the characterization of the strains as insufficient for health claims. However, yoghurt starter cultures, despite not being characterized or defined at a strain level, have an approved health claim in enhancing digestion of lactose in yoghurt in lactose maldigesters (EFSA, 2010). Furthermore, the dossiers should be evaluated by committees that are expert in this domain. Harmonisation between regulatory bodies and clear guidelines on what is needed for which type of approval is essential. An abbreviated IND process, skipping phase 1 studies for strains that are considered GRAS/QPS, would lower the threshold for industry (Hoffmann et al., 2013). It would pave the way for probiotic innovation if regulatory bodies adopt a similar monograph as for natural health products in Canada. This monograph allows certain general and specific claims to be made for certain probiotic strains based on available evidence (Health Canada, 2012). Using such a monograph can reduce unsubstantiated claims and allows avoiding the IND process in specific cases (Hoffmann et al., 2013). An alternative is the adoption of the over-the-counter (OTC) monographs of the FDA for probiotics; these monographs should be harmonised between regulatory authorities.

Industry is heavily reliant on a few strains; there is too much focus on common species (in general bifidobacteria and lactobacilli). By not only choosing the probiotic with the easiest/best growth rate, other organisms with great potential, such as Akkermansia or Faecalibacterium prausnitzii, can reach the market. With increased fundamental knowledge, selection of strains can in the future be based on MoA as opposed to the current process of selection and evaluation through trial-and-error.

It should be noted that as the probiotic market is diverse and contains a wide variety of stakeholders, it is challenging to generalize the barriers. Probiotics have the potential for health and medicinal claims for a wide variety of clinical indications as well as for maintaining a healthy state in individuals. It depends on the intention of the developer, the target population and the applicable regulations which barriers are relevant.

To make a start in repairing the faulty Microbiota Valorization & Technology Transfer Cycle, a single or combined organizational effort can lead the way by using regulatory guidance in order to fulfil the requirements for a health and medicinal claim (Salminen and van Loveren, 2012). Miquel et al. (2015) propose a valuable framework and criteria that should be assessed to obtain a health claim. Market entry of probiotics with thoroughly and fittingly assessed health claims, combined with stricter regulatory enforcement will reduce the market share of unsubstantiated products. This could in turn restore consumer confidence and result in an increase both fundamental as well as clinical research. Such repair of the valorization cycle by overcoming the innovation barriers in the probiotics industry will not only lead to economic benefits, it will also improve general health.
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7.7. References


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