Probiotic Market Developments and Technology Evolution

Cost driven mass markets:
- Dairy commodity marketing
- Culture selection based on milk growth, stability, cost
- Marketing “buzz”, popular perception, folk lore

Market differentiation:
- New, higher value channels
- Innovation based on novel formulation and delivery

Innovation Opportunities:
- Identify groups with specific digestive or other gut issues
- Use new technologies to validate product functionality
- Targeted benefits for demo groups to allow capture of highest added value.
Market segmentation is needed for science based solutions

Key groupings

Chronic conditions

Stage of Life Digestive Health

Transient Risk Factors
Chronic gut conditions are a public health epidemic

Key risk groupings

- Chronic gut diseases have the highest impact on quality of life
- Metabolic syndrome, obesity, and diabetes show correlation with dysbiosis
- IBS is a catch all for multiple conditions but virtually all show dysbiosis
- Selected probiotics and commensals are having big impact on dysbiosis

- Probiotic or synbiotic therapies will be approved and used as drugs
- Commercial development by Big Pharma (Pfizer) & biotech startups.
- Increasing funding by NIH, CDC and other government entities
- Maybe not the best target for supplement or food companies
Age-related digestive and gut issues are increasing . . .

Stage of Life Digestive Health

- Infants - formula fed / high risk
- Elderly - gut senescence
- Menopause - IBS conditions

**Key Risk Groupings**

- Infant formula deficiencies - strong political pressure to improve functionality
- Highest priority for developing world health programs – Gates, World Food

- Elderly populations are highly tuned to their digestive issues - gut senescence
- Nursing home & Medicaid costs are strongly affected by digestive problems.

- Can probiotics help restore Equilibrium microbiota? (EFSA Eldermet Study)
- Stages of life can be targeted without making health or drug claims

- Efficacy, not claims, is key to marketing → consumers want relief
- Ideal category for B-C food and nutrition companies (P&G, Nestle, MJN)
Transient digestive problems are increasing . . .

Key Risk Groupings

- Diarrhea costs are huge in large institutions: schools, hospitals, military
- Problem increases due to centralized food service and larger facilities
- DOD, HHS, CDC, NIH and other programs are looking for solutions

- Foodborne illnesses are a top priority for USDA and FDA – at least 5M cases & 125,000 hospitalizations per year for just the diagnosed outbreaks
- Reluctance to use antibiotics in foodborne infections – poor diagnostics
- Post antibiotic associated diarrhea is largely untreatable – C diff epidemic
- Nonfood probiotic supplements are widely recommended by physicians, but actual results so far are highly variable.

Target Segments

- Schools, Teams, Hospitals
- Military deployments & sites
- Pre-schools and daycare
- Foodborne infections
- Antibiotic therapy
- Traveller’s diarrhea
The healthy human microbiome appears to be conserved . . .

The adult microbiome can now be rapidly profiled → just 3 equilibrium enterotypes were reported in healthy adult humans (based on top 10 taxa)
Gut health issues linked to imbalance in the microbiome

The human microbiome is becoming transparent to ordinary clinicians.

The microbiome can be described at various depths: phyla to strain

Low abundance strains may be responsible for critical functions.

An imbalanced microbiome can quickly recover under normal conditions.

Prolonged microbiome imbalances may lead to chronic health conditions.

Recovery of an equilibrium microbiome may be accelerated by supplementing with selected strains or by fecal transplantation.

Current generation probiotics have only limited impact on the microbiome – they were not formulated or screened for this function.
Evidence for dietary impact on the human microbiome...

Intestinal Microbiota of Breast- and Formula-fed Infants

Breast-fed Infants

Formula-fed Infants

% of total flora

Effect of HMOS

0 10 20 30 40 50 60 70 80 90 100

days

Bifidobacteria
Bacteroides
E. coli

0 10 20 30 40 50 60 70 80 90 100

days

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Genomics offers a view of the human microbiome and its functions

16S rRNA genes → Extract DNA → Extract RNA → Extract Protein → Extract Metabolites

- Microbiome: Microbial communities
- Metagenome: Total genetic composition
- Meta-Transcriptome: Picture of all expressed genes
- Meta-Proteome: Expressed enzymes
- Meta-Metabolome: Expressed metabolites
Finding the microbes responsible for health or dysbiosis . . .

Willing et al., Gastroenterology.2010
Microbiome profiles are diagnostic for IBS subtypes

“Microbial Disease Signatures Characterize the Gastrointestinal Microbiomes in Irritable Bowel Syndrome”

We were able to correctly classify all cases of IBS subtypes using a limited set of discriminant bacterial species.

This study suggests that stool microbial 16S rRNA metagenomic analysis identifies pediatric IBS-associated signatures and facilitates categorization of pediatric IBS subtypes.

Preliminary acceptance for publication in Gut
Probiotics can alter the abnormal microbiome in IBS

“Conclusions: The probiotic supplement was thus shown to exert specific alterations in the IBS-associated microbiota towards the bacterial 16S rDNA phylotype quantities described previously for subjects free of IBS.”
Probiotics are now used regularly by GIs in IBS

• 98% of surveyed gastroenterologists believe probiotics have a role in treating GI symptoms
• 93% of gastroenterologists have patients taking probiotics for IBS symptoms
• Physician practices do not correlate with published, expert-supported guidelines

There is a lack of good data on probiotic effects, but it is often the only tool that doctors have - antibiotics are no longer the magic bullet.

“Conclusions: Effective implementation ... will benefit from additional supporting studies and the eventual development of clinical practice guidelines supported by the major gastroenterology societies.”
But the results with existing probiotics in IBS are mixed

“Conclusion: Probiotics appear to be efficacious in IBS, but the magnitude of the benefit and the most effective species and strains are uncertain.”
### Limitations of 1st generation probiotics

#### Original selection criteria were ill-defined:
- Most strains were selected for ability to grow in milk
- Selection often based on folkloric associations
- Gen 1 strains are still treated as magic bullets for health
- Only a small number of strains are commercially available

#### Bioavailability & potency of commercial products:
- Many products have little GIT impact as formulated
- Cells die in the formulation - low counts at point of ingestion
- Up to 99.9% of ingested cells are destroyed in the stomach
- The GIT constantly sheds its mucin layers
- Probiotics need nutrients in order to persist

#### Health claims & proof of efficacy
- High hurdles for health claims - multiple studies often conflict
- Gen 1 probiotics were not selected for the targeted benefits
- Beneficial effects are often objective & difficult to measure
- Enumeration methods do not give a picture of gut impact

#### Generic marketing strategies
- Mass marketing reduces likelihood of real benefits / claims
- Money is mostly spent on marketing - not enough on science
- Dairy is losing out on emerging segments with targeted needs
New strain libraries will be developed based on genomic tools . . .

Development of new gut health strain libraries is in the early stages

→ Next generation of diversity has moved beyond Gene Libraries
→ Existing strain libraries need to be genomically characterized
→ How much novelty vs existing strains?
→ Presence or absence of key genes related to gut function?
→ Unfortunately, the biodiversity of existing collections may not be enough

Sequencing of Existing Collections

Annotated & Searchable Strain Banks

Presence or Absence of Key Genes
New strain libraries will be developed based on genomic tools . . .

Development of new gut health strain libraries is in the early stages
- Go back to nature to pull out low abundance probiotics
- New enrichment tools can pull out low abundance, high impact strains
- Use of different types of milk for enrichment stage
- Omics based gene and strain hunting (e.g., niche growth factors)

**Flowchart:**

- **Sequencing of Existing Collections**
  - **Annotated & Searchable Strain Banks**
- **De novo Probiotic Screening**
  - **Cow, pig, human milk enrichments**
  - **New Probiotic Diversity Libraries**
New strain libraries will be developed based on genomic tools . . .

Development of new gut health strain libraries is in the early stages
→ Next generation of diversity needs to include allochthonous bacteria
→ The new libraries will be built by foundations, agencies, & industry
→ Goal is broader access to the deep biodiversity of human GIT
→ Focus on populations resistant to pathogens and nutritional deficiencies
→ Thousands of new strains and genes are likely to be found!

- Sequencing of Existing Collections
  - Annotated & Searchable Strain Banks

- De novo Probiotic Screening
  - New Probiotic Diversity Libraries

- Global mining of high resistance populations
  - High Impact Commensal Libraries
From Probiotics to Synbiotics

Tap into Biodiversity

Screen the most robust microbiomes

• deep dive enrichment
• sequence mining
• robust microbiomes

New Strain Libraries

New Dairy Prebiotics

Targeted Synbiotics
Metabolomic profiling – Lawrence Berkeley Lab
The future of Milk based Synbiotics . . .

Processed foods are severely limited as delivery systems
→ Less acceptance of live cultures in processed foods
→ Limited ability to deliver high potency, viable strains
→ Poor support matrix for survival, growth & persistence
→ Nevertheless, some success in novel targeted foods

Dairy Products have many advantages
→ Better potential to deliver high counts at point of ingestion
→ Better potential to deliver more active strains at ingestion
→ Good survival in the upper stomach due to milk buffering
→ Lactose can support growth in the Small Intestine
→ Dairy prebiotics support growth in the Large Intestine

New synbiotic formulations for dairy applications. . .
→ High potency DVI’s can simplify processing & ensure counts
→ Select prebiotics to match the strain & ensure persistence
→ Tailor starter cultures around the probiotics - sales boost
→ Cross over studies with microbiome profile as biomarker
Probiotic and Gut Health Markets in 2020

Market Positioning

Differentiated Segs

Mass Markets

Generic ➔ Proprietary Strains

→ Prebiotics ➔ Microbiome Solutions

Generic Supplements

Dairy Products

Bars & Foods

Infant Formula

Specialty Supps

Drug Tmts

Geriatric Foods

Technology Continuum

DSM