مرکز رشد واحدهای فناوری فرآورده
های دارویی

Production Of Probiotic supplements

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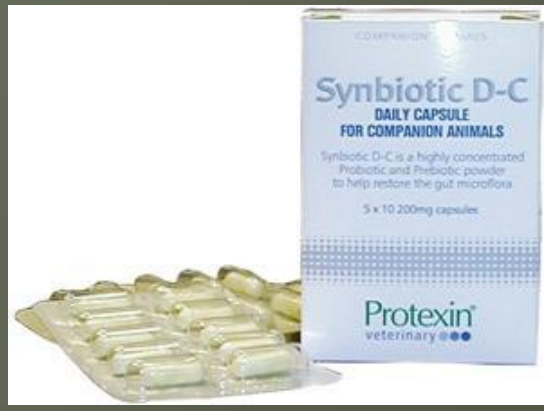
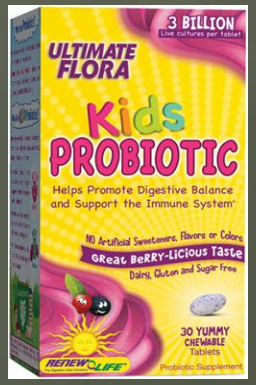
Definition

- Dietary supplement containing live bacteria that replace or add to the beneficial bacteria normally present in the gastrointestinal tract
- A daily intake of 10^6 to 10^9 viable organisms would be effective

Dosage forms

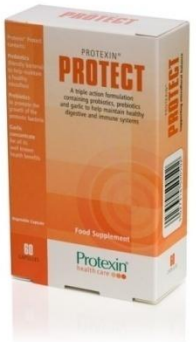
1) **Oral Capsule:** the most popular dosage form
2) **Oral drop:** Convenient use for infants
3) **Powder/sachet:** allow consumers to pour the powder into their favorite food
4) **Chewable/Ec Tablet:** for children with various strains, shape, size, and flavor.
5) Enteric coating give more reliable resistancy to gastric acid and bile.
6) **Vaginal capsules:** for vaginal use
7) Dermal products





Implying some brands

- ***Protexin*** **products:**
- *Capsule:*
  - Balance: *For teenagers and adults*
  - Balance+: *specially for the over-50s*
  - Protect: *For times of extra need*
- *Sachets:*
  - Restore: *For babies and very young children*
- *chewable tablets:*
  - Vitality: *For children aged 4+*



- ***BioGaia*** products:
- *Oral drop:*
  - ProTectis drops D3: *Lactobacillus reuteri* + *Vitamin D3*
  - ProTectis drops: *Lactobacillus reuteri*
- *Sachet:*
  - ProTectis ORS: *Oral Rehydration Solution with Lactobacillus reuteri*
- *chewable tablets:*
  - Strawberry and lemon flavour
- *Lozenges:*
  - slowly melt in your mouth

Photo : Hamed Jafarnejad

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Production process

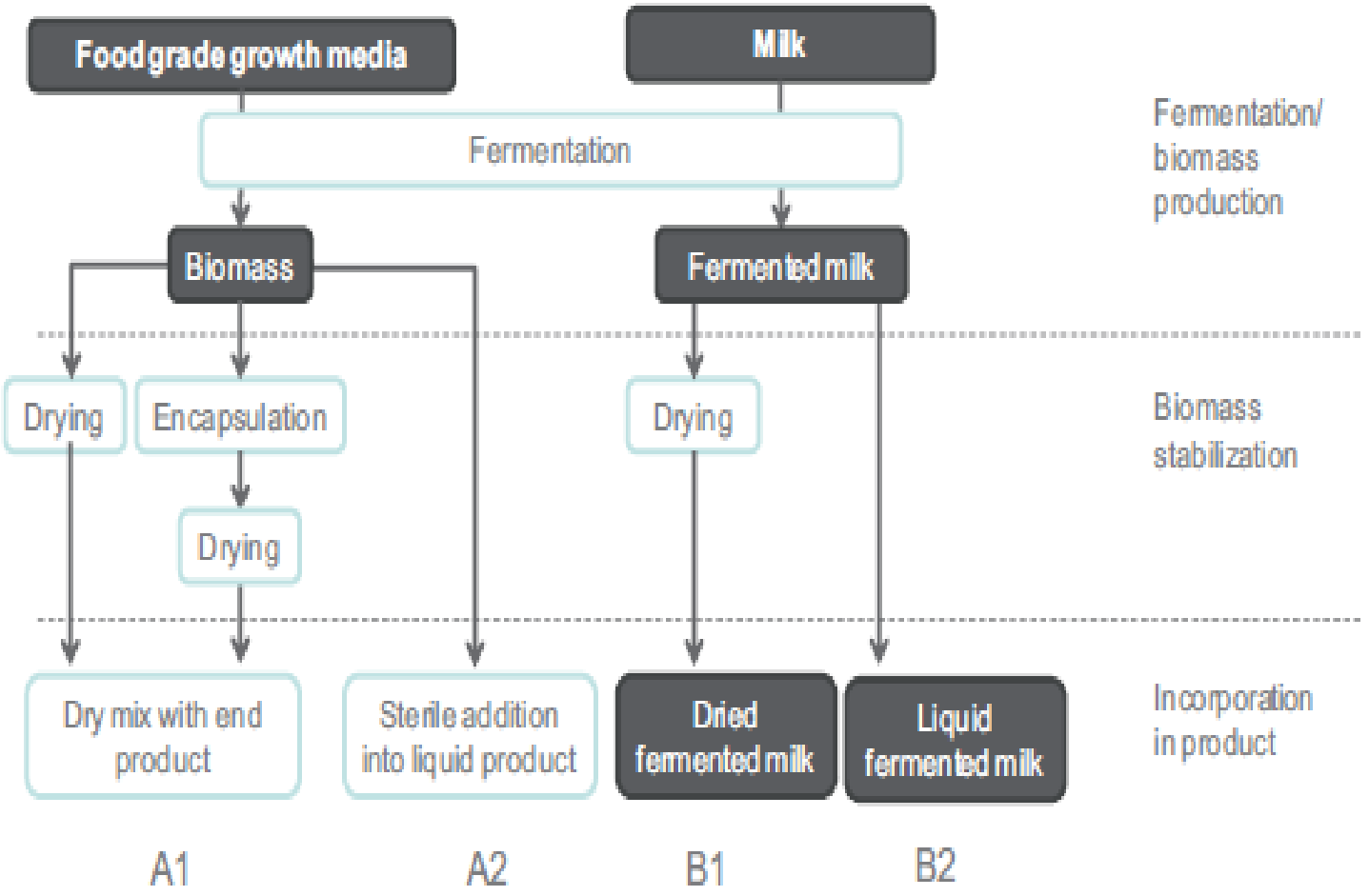

Fig. 1. Schematic routes of production and incorporation of probiotics into different types of food products.

Drying methods

- Freeze-drying the leading technology for drying probiotics:milder conditions that help maintain high level of cell viability
- spray- or vacuum-drying have been gaining increased attention as attractive probiotic drying methods :lower operating costs and higher throughput capacity at acceptable level of probiotic survival


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Important considerations in the production of probiotics

- Usage of protective agents and encapsulation of probiotics are the most important points
- The currently available protective matrices fall into two groups.

1. Complex/semi-defined mixture of ingredients (skimmed milk)
2. Defined single ingredients e.g. sugars such as mono-, di-, or oligosaccharides)/ sugar derivatives such as sorbitol / a defined mixture of ingredients containing low- and high-molecular weight sugars as their basic component

- In addition to sugars, an antioxidant may

be necessary to reduce oxidative damage during drying and storage

- Proteins
- amino acids
- prebiotics/fibers

used individually or mixed

“positively impact the drying- and storage-stability of lactic acid bacteria”

Storage stability of probiotics

- In general, maintaining probiotics at low aw improves storage stability
- Depending on **the storage conditions** and **duration**, loss of probiotic viability during **storage may be higher** than loss during drying
- Low aw is easily achievable in supplements, which probiotics are typically the only active ingredient, dried to a very low aw, and enclosed into a moisture-tight capsule

Quality control tests on finished product

- Physical (appearance,taste,..)
- Biochemical (pH, water content, viability, heavy metals,..)
- Microbial limit tests
  - total counts (non lactic)
  - yeast & mould
  - enterobacteriacea,
  - *Bacillus cereus*
  - Clostridia
  - Pathogens including :*E. coli,S. aureus,L. monocytogenus*
  - *,P. aeroginosa*, salmonella)

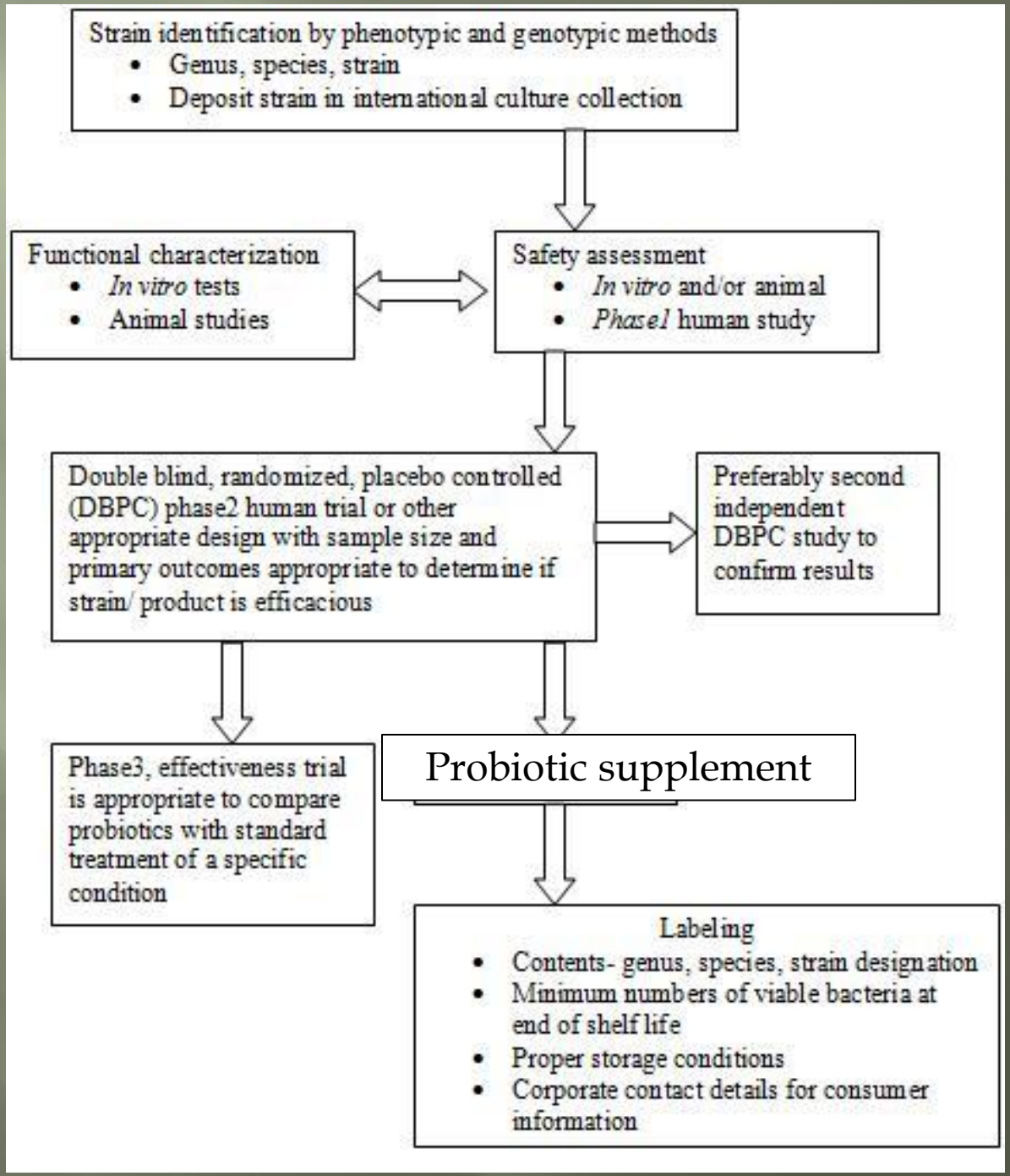
HACCPS

- Water is controlled for bioburden or sterility
- Air is controlled for bioburden and nonviable particulates
- Component materials may require sterilization before use and should also be monitored for bioburden
- Product contact equipment should be sterilized, or sterile disposable equipment can be used
- All areas and surfaces in the manufacturing environment where open steps are performed should be monitored for bioburden
- Cleaning and disinfection and prevention of cross-contamination with other products manufactured in the same areas
- Multiple products never be manufactured in the same areas at the same times

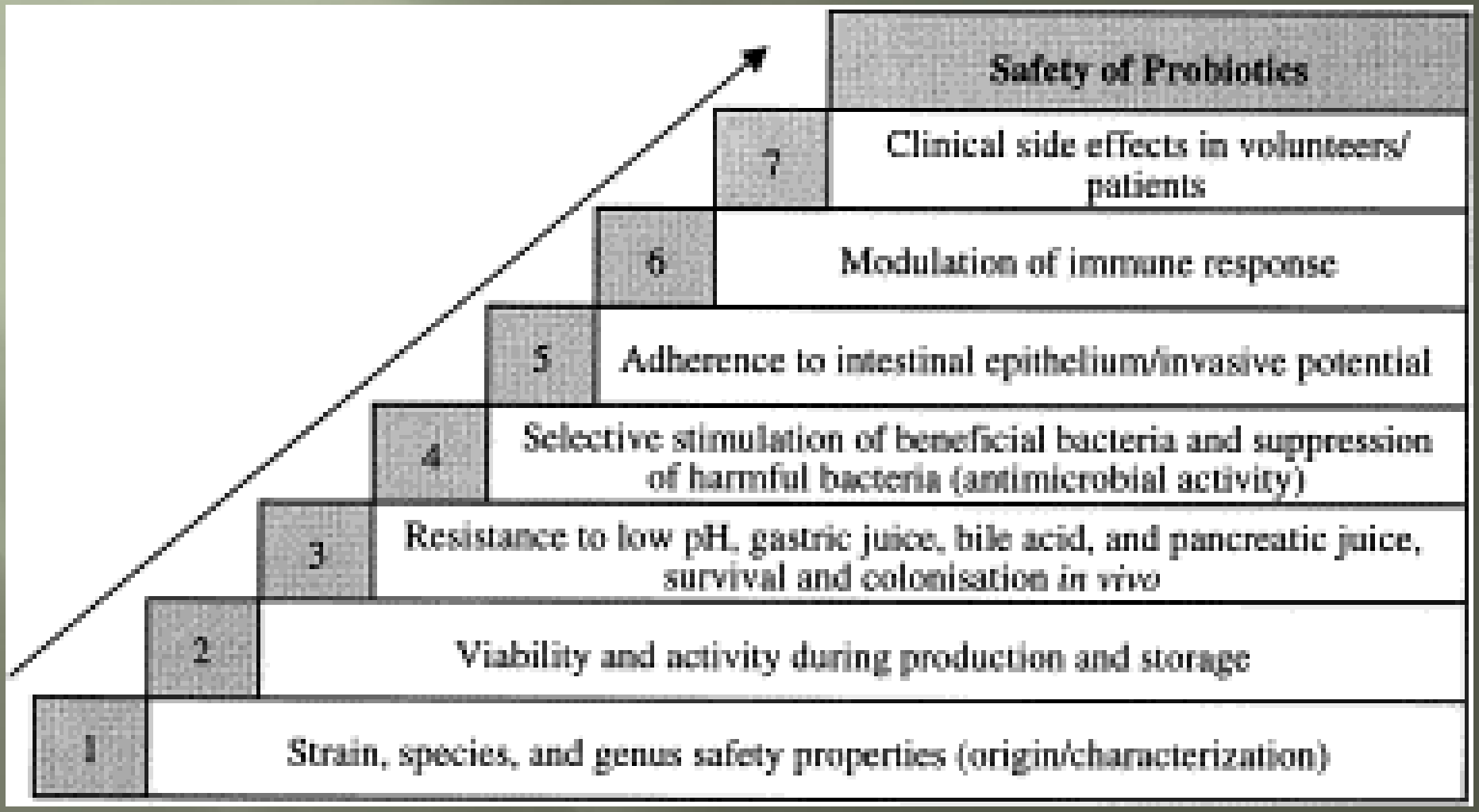
Pathway for a biologic new drug

- similar to new drug.

1. **Discovery**
2. **nonclinical safety testing precedes clinical safety testing**
3. **efficacy testing**


Strain identification by phenotypic and genotypic methods
Genus, species, strain
Deposit strain in international culture collection
Functional characterization
In vitro tests
Animal studies
Safety assessment
In vitro and/or animal
Phase1 human study
Double blind, randomized, placebo controlled (DBPC) phase2 human trial or other appropriate design with sample size and primary outcomes appropriate to determine if strain/ product is efficacious
Preferably second independent DBPC study to confirm results
Phase3, effectiveness trial is appropriate to compare probiotics with standard treatment of a specific condition
Probiotic supplement
Labeling
Contents- genus, species, strain designation
Minimum numbers of viable bacteria at end of shelf life
Proper storage conditions
Corporate contact details for consumer information

Development of probiotic supplement



in vitro safety & functionality aspects should be checked

Genetic stability/genetic transfer

- assessment of a strain's genetic stability requires the availability of its whole-genome sequence.
- based on genotypic **comparisons** between re-isolates of a given probiotic strain throughout the course of production

Assessment of Antibiotic Resistance (In case of suspected acquired resistance or intrinsic resistance, transferability tests are Optional)

Adhesion to Caco2

Tolerance to Gastric juice

Surviving in different salt and temperature conditions

Antimicrobial activity against pathogenic bacteria

Bile salt resistance

Resistance to spermicides (Applicable to probiotics for Vaginal use)

Strains selection for "drugable" target

- In vitro tests results (which lead to certain benefit)
- Preclinical studies
- different review articles in human
  - *L. reuteri* DSM17938 has been shown to significantly reduce crying time in colicky babies, possibly by improving gastric emptying
  - *L. reuteri* NCIMB 30242 (Cardioviva™), was developed as a cholesterol-lowering probiotic based on its high level of bile salt hydrolysis (BSH)

Importance of phase3 studies

It is also important not to assume that a probiotic strain shown to be health beneficial when administered alone, has the same benefit when administered in combination with other Strains.

so

any novel mixture of probiotic strains, even if it contains a well-studied probiotic strain, should be substantiated in a separate set of studies

Labeling

- The suggested serving size must deliver the effective dose of probiotics related to the health claim
- Minimum viable numbers of each probiotic strain at the end of the shelf-life
- Health claim(truthful descriptions of documented benefi)
- Proper storage conditions
- Corporate contact details for consumer information
- Genus, species and strain designation (Strain designation should not mislead consumers about the functionality of the strain)

Thanks for attention