INTERNATIONAL PROBIOTICS ASSOCIATION EUROPE

Brussels, 7 September 2022

IPA Europe representing the probiotic food and food supplements in Europe acknowledges the European Commission's proposal on Blood, Tissues and Cells and welcomes the opportunity to participate to this consultation.

The Substances of Human Origin (SoHO) framework applies on the first activities in the chain (donation, collection, testing). The subject matter and the scope of application of the regulation, as indicated in the 'general provision' recognise the importance of ensuring safety and quality of SoHOs that are not defined by the terms 'blood', 'tissue' or 'cell', such as breast milk and intestinal microbiota. The scope is therefore defined by the broader term SoHOs.

IPA Europe members see a risk of confusion, since the SoHO proposal of Regulation could unintentionally have an impact on microorganisms used for food production. We therefore would like to contribute to the consultation in providing useful information that can help to distinguish the activity of isolation of probiotic strains and the regulatory references that already apply to them.

Potential probiotic strains isolated from humans are not to be considered under the scope of SoHO or to be regarded under the definition of "SoHO preparation".

Regulatory, Industry and country guidance require, inter alia, that probiotic strains must be sufficiently characterised and safe for the intended use – irrespective from where they are isolated. [1] [2] [3] [4]

The activity of isolation of probiotic strains kept in culture collections / research cell banks (for food purpose) is out of the scope of SoHO as their initial intended use is research, which is exempted as per point (17) of the Preamble. Since the intended use of the isolated strain before collection is research, the deposited strain should not be considered a SoHO.

- The isolation and deposit of strains from a microbiome sample that are not pre-destined for ingestion by humans without further evaluation as a suitable probiotic conferring a health benefit (and corresponding characterisation and safety assessment) should not fall under the scope of SoHO or be regarded under the definition of "SoHO preparation".
- Isolation and deposit of microbial strains in international or research collections is a 'research activity' which is excluded from the scope of SoHO as per point 17 of the Preamble. The potential use (industrial, medicinal, cosmetic, food, feed etc.) of the isolated strain before collection and deposit is not pre-determined and unknown. Any possible future use in human would be preceded by several steps including full characterization and safety testing (no associated risk).

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Single bacterial strains with potential probiotic properties isolated from human microbiomes are not to be regarded of human origin (as targeted by the scope of SoHO); in addition, they are not human cells/do not contain human material.

- Single strains isolated from a microbiome sample for research are not generated by a human being (no human DNA, no human "signature", cells or material); in addition, they are not pre-destined for ingestion by humans as such, or; in this case, human beings are a reservoir of microorganisms which originate from external sources (e.g. soil, diet..); this is not comparable to the case of FMT in terms of donor specificity or safety obviously.
- Further characterisation and safety assessment and evaluation of characteristics of the strain for suitability, including as a probiotic conferring a health benefit, must follow before such an isolated strain is considered for development for use in a food or food supplement (or indeed as a Live Biotherapeutic Product, LBP).
- In addition, the IPA Europe/ISAPP criteria for qualification as a probiotic requires that a strain must be supported by at least one positive human clinical trial conducted according to generally accepted scientific standards, or as per the recommendations and provisions of local/national authorities when applicable [3,4.]
- Bacterial strains which are present in the respiratory tract, vagina, skin, gastrointestinal tract originate in the external environment - humans are the host, but not the origin of these bacteria.
- The principles of Food Law require that, irrespective of the origin, food shall not be placed on the market if it is unsafe (injurious to health, unfit for human consumption) - it must be safe and suitable [5].
- This principal is already built into regulatory requirements, including for Novel Food where EFSA assess the safety of novel microorganisms (without a safe history of use) used in food before they are authorised for use in the European market [6]. The qualified presumption of safety (QPS) concept was developed in 2003 to provide a harmonised generic safety assessment of microorganisms [7,8].
- Informed consent is part of Good Clinal Practice[9].
- Live Biotherapeutic Products (LPBs) the use of single strains in human is already covered by the quality requirements for therapeutic use where medicinal products contain live micro-organisms (bacteria or yeast) for human use[10].

General comment about research and innovation. Isolation and deposit of microbial strains in international or research collections is a research activity. If the intention is to already indicate the SoHO entity status at the beginning of the process, this will completely block innovation due to the high burden it will require, and there is no justification for that, as the risk is mitigated by the isolation procedure.

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Consistency with other provisions in the policy area. It is stated in the proposal that the SoHO framework applies on the first activities in the chain (donation, collection, testing) while these later activities (manufacturing, storage, distribution etc.) are regulated under these other appropriate legislative frameworks (e.g. medicinal products, including advanced therapy medicinal products, or medical devices." Probiotics are under Regulation (EC) 178/2002 that do not cover the medical terms.

We also would like to clarify some aspects in relation to the activity of isolation of probiotic strain to avoid any confusion with the "faecal microbiota transplants" activity/definition. Page 4 Ex-post evaluations/fitness checks in the current proposal: "*…it is not clear which of the BTC Directives apply, leaving these substances unregulated or regulated in divergent ways (e.g., breast milk and faecal microbiota transplants)*." For clarification, the activity of isolating a single microbial cell, comply with the safety requirements; multiply it by fermentation, concentrate, dry, formulate, pack, distribute and sell it as "probiotics" is different from the definition "faecal microbiota transplants".

For information, a "faecal microbiota transplants", contain approximately 100 gram or more of faeces with 10^9 microorganisms/gram, meaning a mixture of totally around 100 billion of several thousand different microorganisms. This is very different from probiotics single strain products.

From page 100: the quality system "require traceability from donor to recipient and vice-versa". This cannot apply to probiotic food products.

Alignment with other EU regulation. This interpretation is aligned with the Regulation (EU) No 511/2014 on the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilisation in the Union,[11] where human cells are exempted from access and benefit sharing, but where this is not the case for isolates from the human microbiome, because these are not regarded as human cells and considered of non-human nature. If sampling from human microbiome for probiotics are considered "not of human origin" for Access to Genetic Resources and Benefit Sharing, then the same should apply to SoHO. In fact, the Guidance document on the scope of application and core obligations of Regulation (EU) No 511/2014 on the compliance measures for users from the Nagoya Protocol[11,12] states:

- Page 9: "Human genetic resources are out of the scope (of the Nagoya regulation)"
- Page 12: "While associated with human beings and essential for the well-being and survival of human individual, the human microbiome represents resources of non-human nature"
- Thus, on Page 13: "4. Testing of *Lactobacillus rhamnosus* for use in probiotics. …isolated from samples taken from different human individuals and as such is considered to constitute utilisation in the meaning of the EU ABS Regulation".

Conclusion: based on the information provided above and on the fact that the activities of manufacturing, storage, distribution etc. of probiotic strains are regulated by other appropriate

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legislative pieces, and that microbiome isolates are not regarded as human cells or of human nature, we consider that the single strains isolated post collection from microbiota and kept in culture collections/research cell banks of microorganisms are excluded from the definition of «SoHO preparations» collected from the human body.

Thank you for your attention. We remain at your disposal for any clarification you may require.

Best Regards

Rosanna Pecere

References

[1] Ministero della Salute Guidelines on Probiotics and Prebiotics Revised in March 2018

[2] Swiss Ordonnance du DFI sur les compléments alimentaires (OCAl) 817.022.14 Annex 3

[3] https://www.ipaeurope.org/wp-content/uploads/2021/06/IPA-EU-Manifesto-2021.pdf

[4] https://www.ipaeurope.org/wp-content/uploads/2021/09/2020-7-27-IPAEU-Probiotic-Criteria.pdf

[5] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety

[6] EFSA Guidance on the preparation and submission of an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283 - 1.9.7.2 Microorganisms

[7] EFSA topic on QPS: https://www.efsa.europa.eu/en/topics/topic/qualified-presumption-safety-qps

[8] EFSA BIOHAZ Panel (European Food Safety Authority), 2022. Update of the list of QPS-recommended microbiological agents intentionally added to food or feed as notified to EFSA 16: suitability of taxonomic units notified to EFSA until March 2022 **https://doi.org/10.2903/j.efsa.2022.7408**

[9] DECLARATION OF HELSINKI – Ethical Principles For Medical Research Involving Human Subject

[10] European Pharmacopoeia General Monograph 3053; Chapter 2.6.36; 2.6.38

[11] Regulation (EU) No 511/2014 of the European Parliament and of the Council on the compliance measures for users from the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilisation in the Union

[12] Guidance document on the compliance measures for users from the Nagoya Protocol

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