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One Science, Three Regulators: What the Metabolite Turn Means for Microbial Products

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The argument is that probiotics, postbiotics, synbiotics and live biotherapeutic products have become a scientific continuum while remaining separate regulatory categories



The same microbial preparation can reach an Indian consumer as a food, as a nutraceutical, or as an investigational medicine. The science underneath does not change. What changes is the evidence asked of it, the authority that asks, and the claims the label is then permitted to carry.

For most of the past decade that was tolerable. Probiotics were live organisms sold as supplements, medicines were medicines, and the ground between them was wide enough that few products had to stand in it. Then the field moved, and it moved in a particular direction.

The turn from organism to metabolite

Much of what the microbiome does for its host, it does chemically. Bacteria ferment what we cannot digest and release compounds the host then uses, and those compounds are increasingly understood to be where the physiology actually sits.

Butyrate is the best characterised of them. It is a short-chain fatty acid the human body does not synthesise, produced by colonic fermentation of dietary fibre, and it is the principal energy substrate of the colonocyte, a role Roediger described in 1980. It supports tight junction assembly, modulates histone deacetylase activity and regulatory T-cell differentiation, and acts on the free fatty acid receptors FFAR2 and FFAR3 on enteroendocrine cells, where it influences incretin secretion. A single bacterial metabolite, carrying a substantial share of what we attribute to a healthy gut.

Once that is understood, an obvious question follows. If the metabolite is doing the work, why supply the organism and hope it is produced?

That question has produced a generation of products built on microbial metabolites directly, and it is the reason our categories no longer hold.

Where the categories stopped being distinct

A probiotic is a live organism administered in adequate amounts to confer a health benefit. A postbiotic, under the 2021 consensus, is a preparation of inanimate microorganisms or their components. A synbiotic combines organism and substrate. A live biotherapeutic product is, in regulatory terms, a medicine made of bacteria.

As a list, four tidy categories. In a development laboratory they are points on a continuum, with products at every position along it. Heat-treated strains. Cell-free supernatants. Defined consortia selected for one physiological effect. And purified metabolites with no cellular material in them at all, including butyrate delivered as tributyrin, a triglyceride prodrug cleaved by lipases along the gut rather than absorbed as a salt in the proximal intestine.

A formulator moving along that continuum is making a scientific decision about mechanism. They are also, often without intending to, deciding which authority will govern the product and what it will cost to prove anything about it.

Definitions written for an earlier generation

The consensus definitions are good documents, carefully argued and widely adopted. They were also written to describe the products that existed when they were drafted.

The postbiotic definition shows this most clearly. It requires inanimate microbial cells or their components, and deliberately excludes purified metabolites containing no cellular biomass. That exclusion was reasonable and remains defensible. It also means that products built on precisely the molecules through which the microbiome is now understood to act fall outside the term most commonly used to market them.

This is not pedantry. A definition determines which literature a company may cite, which pathway it enters, and what a regulator will accept as evidence. Where a product sits outside every available definition, those questions have no settled answer, and the answer tends to be supplied by whoever is most confident rather than whoever is most correct.

The real cost is to the standard of proof

When a category's boundaries are unsettled, the evidence bar attached to it drifts downward. A company that commissions a registered, prospectively declared trial competes on the same shelf as one that cited an ingredient supplier's literature and called the matter settled. Both may use the same category word. Nothing on the label distinguishes them.

Three things would help, none of them requiring a regulator to move first. Describe products by what they contain rather than by the category word that sells best; a purified metabolite is a purified metabolite. Register trials prospectively, including small ones, and publish them including the ones that disappoint. And settle measurement before settling claims, because for metabolite-based products our endpoints are presently weaker than our chemistry.

India has the clinical infrastructure, the manufacturing base and the research capacity to lead this category. What it does not yet have is agreement on what the category is. That is worth settling ourselves, and soon.

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