EU Regulatory Framework for Microbiome Product Development
Questions and Answers from the Ask the Experts session

Microbiome-based products can fall under several regulatory statuses, in both the food and medical arenas. As each of these regulatory statuses represents specific benefits and constraints, and will directly impact the cost, timeline of the development, it's critical for the developers understand the regulatory framework of microbiome-based products.

Our Experts

- **Clara Desvignes**, **MSc**, supports life science companies in the development and implementation of global regulatory strategies for medical devices, combination products and drugs. She manages projects involving microbiome-related technologies and provides guidance on the regulatory, nonclinical, clinical and CMC related activities.

- **Peri Aghadiuno, MBBS, MRCOG,** has +10 years of experience in clinical development planning and plays a key role in identifying appropriate questions for Regulators as part of the requests to EMA, National Agencies and joint EMA-HTA bodies for scientific advice. Peri was Senior Medical Assessor at the MHRA for 10 years and provided scientific and regulatory advice to companies before and after the submission of their applications.

Question: Given that Live Biotherapeutic Products (LBPs) are quite innovative, is there a regulatory agency more experienced with the evaluation of this product?

[Live biotherapeutic products (LBP) are medicinal products containing live micro-organisms (bacteria or yeasts) for human use. LBP are administered orally or vaginally and are available in different pharmaceutical forms. LBP may contain one or multiple microbial strains from the same or different species of micro-organisms.]

VCLS Answer: There are two main geographical areas to mention, firstly the US which is a key region, not just for the development of LBPs, but also for microbiome product technology in general, and also the EU. As per the EU side we don't have one general process for all these products, so there might be discrepancies between the expertise of different agencies. We can mention a few with expertise on microbiome related products either because they have participated in the evaluation of clinical trials related to microbiome technologies or because they have given some scientific advice to developers. For example, Sweden, Germany, Spain, France and Italy, and although it's not technically part of the EU anymore, it is important to mention the UK as they have strong expertise around those products.

Not only should you consider the agency's expertise on microbiome products in general but also consider the expertise they have in the therapeutic area and the

type of technology you are working on. For example, if you are working with genetically modified organisms, this can be a priority area to look at as well, so this forms part of a big picture in determining which agency you are going to talk with regards to the development of your product.

Question: Could you please comment on the requirement for shedding studies where the LBP is genetically modified?

VCLS Answer: The most important thing to note is that it's been genetically modified, and we must be careful to remember the regulatory framework. We do have a regulatory framework, we have a monograph, Live Biotherapeutic Products, also have the EUPharm. However in terms of guidelines for nonclinical and clinical, there are no specific guidelines yet. I would take the ATMP guideline as my first base. It's imperative you conduct the studies using the guidelines in place. If you do not have any guidelines in place, it is a good idea to seek scientific advice from many of the big agencies already mentioned.

Question: Which regulatory framework should be followed for the development of an LBP for gene therapies in EU countries?

VCLS Answer: We must be careful here as different frameworks may apply for the product depending on the type of product you have. The first step is to understand the classification of your product. At the very early development stage I would recommend seeking confirmation for the classification of your product. This is because even though we have the monograph and the European Pharmacopoeia, we don't have an LBP Guideline like the US. Therefore, I would first want to understand how the EMA may view my product so I would apply for CAT classification to get an understanding of where the product lies so I know which path to follow.

Even though we have the LBP terminology established in EU it does not cover gene therapy agents, this is where there may be an overlap or difficulties in how they will be regarded by the agencies. One point regarding GM organisms, which is another regulatory framework to consider would be part of your development, especially for clinical trials, so you should pay attention to those aspects during your development, and this may vary a lot at the national level as well.

Question: What advice would you give microbiome-based product developers who would like to reference the QPS status when documenting safety information for a LBP product?

VCLS Answer: A Qualified Presumption of Safety is a status defined by EFSA (European Food Safety Agency). A key point to highlight is in the EU there is not much interaction between the EMA and EFSA. It's a separate agency, so there's no direct transition in terms of the safety from the food side to the therapeutic drug side. It's important to understand that although it's not direct, you may be able to re-use some of the elements that were supportive of your qualified presumption of food safety and to incorporate them as part of your drug dossier. It's important to capitalize on the previous data that has been generated on your product for its use under the therapeutic field.

The requirements with regards to safety for a food product, differ significantly to the requirement for a medicinal product. So, if you are making the shift from being a food product to a Live Biotherapeutic Product, even though you have all the presumption of safety from a food perspective which would be supportive data, you will have to conduct robust studies before you can even go into a First in Human (FIH) study. You would probably have to repeat nonclinical studies and complete nonclinical studies in line with regulatory requirements under ICH principles which is a requirement before you can conduct a FIH.

However, I must point out anything that has been gathered and accumulated on the product when it was a food product would help with the safety of the product if the product has not changed significantly from being a food product to being a microbiome therapeutic product, so you can leverage the data from the food product as supportive data.

Question: Would a 'FIH' study for a microbiome product have to be conducted in healthy volunteers or can a study be initiated straight away in patients?

VCLS Answer: Fundamentally the principles of clinical development for small molecules or biological molecules are applicable for microbiome products. However, there may be differences in the approach to clinical development of microbiomes due to their nature.

There are different aspects to consider including the type of product, therapeutic area and intended indication.

ATMP guidelines could probably be applicable in this situation as no real clinical guidance in place for microbiome products in Europe as of now (acknowledging that there is a general monograph in place and the chapters in the Ph Eur).

It may be necessary to go straight into patients depending on indication and type of product :

- The complexity, product characteristics should be considered (persistence in humans, side effects, immunogenicity
- Ability to extrapolate from animal data
- Dose considerations

When doubt in the development seek scientific advice early on – get an idea of what they would prefer.

Clara and I have had cases where clients have conducted studies in Europe in healthy volunteers where people have gone ahead and asked FDA, who would clearly say 'no', this is a live biotherapeutic product you shouldn't be administering it to healthy volunteers rather the product should be administered only to patients. I must say that views differ from country to country in Europe so you may find some agencies that will think it's not likely to be of harm if given to a healthy volunteer and they may be happy for you to conduct a study in healthy volunteers. For me, I would say in most cases think of conducting studies in patients directly.

Question: Do LBPs have to be regulated as medicinal products or can they be regulated as probiotics?

VCLS Answer: One important point to identify is terminology because when we talk about LBPs from the regulatory perspective they are considered as medicinal products by definition. There is often confusion between the term of 'LBP' and that of probiotics, which is something more general and is not as clearly set in the regulatory framework either as food or drug. So typically, whether your product has pharmacological action or immunological one or metabolic action, this will be what we call an LBP so with a therapeutic purpose, typically evaluated as a drug.

It's also possible your product has benefits but it's incorporated into food and it's not for any treatment or prevention of disease, and has general health benefits. In that case it can be used in foods, and it can be qualified as a probiotic if you have the ability to demonstrate your product provides health benefits. However, those are two different frameworks and although the terminology is not that clear those two may be relevant for the development of live based technologies for human benefit.

- LBP by definition "therapeutic"
    - *Medicinal products normally have pharmacological action, probiotics do not have any pharmacological function, they are for maintaining health and balance i.e. just a health claim*
- No "probiotic" regulation or status, but live microorganism can be developed under the nutraceutical framework under a variety of statuses
    - *Probiotics are not regulated as medicinal products, they are usually commercialised via notification or self-determination*

Question: Could you provide some examples of the endpoints which can be used to evaluate the impact of a product on patients' microbiome?

VCLS Answer: The endpoints depend on the therapeutic areas, patient population, and on the claim you're determined to make at the end of it. For early clinical development you may want to choose a biomarker to be able show your product works in the way that it should work. You want to use a biomarker to determine your pharmacodynamic activity and in later on in development towards confirmatory trials, you may want to correlate that biomarker with the endpoint indicative of efficacy. I can't really say that there is a specific end point to be investigated, it would be dependent on your therapeutic area, targeted indication, patient population but obviously clearly in early development you need to get that biomarker that will be determinative of efficacy which you're going to correlate later on as a clinically robust endpoint.

Question: You mentioned the microbiome product can be regulated as a drug or food. How about medical devices, are there any regulatory limitations to incorporate bacteria in a medical device cream?

VCLS Answer: We tend to talk about drugs and food a lot but it is possible to have microbiome related application as part of medical devices. May be one key point is recently we have had a new regulation put in place for a medical device and it has provided a specific statement around the presence of live microorganisms that may contribute to the mode of action, and this is not possible any more for medical devices. This means in practice if you have a medical device and you want to

incorporate bacteria because it will improve a piece of your product, it's only possible where the product is nonviable as part of a medical device or does not have a contribution for the intended purpose. In that case you can incorporate this type of element in your device its very likely to have an impact on your risk classification so this will be a key aspect to consider as part of your development. More generally when you incorporate this item in your device, if it's a cream for example, what impact the microorganism on the efficacy or stability of the product so all of these aspects will need to be considered as part of this development.

Question: Could you please provide some information about the GMO framework for microbiome product development?

VCLS Answer: The GMO framework is to be considered as part of your development, it's something which is distinct from the typical medical framework but still applies if your product is in development. This is something you will have to consider during clinical development, and which may apply and in practice differently between the country you will be working with. In some cases, you will work in 'deliberate release' environment while in some cases it's 'contained use' depending on how you control the liberation of the organism you are working with in the environment. So really here it's something which is distinct from what we usually call as part of the development of clinical trials and you may have to work with other agencies that you would typically mention for clinical trials because in that case you could have authorities from the Environment Ministry or agriculture ministry involved as part of the assessment.

The important point to understand is there are different national requirements so the GMO framework is a bit different, you have the EU as the top most but as you come to the GMO you have to understand the national requirements from each country.

Question: Could you please give examples of LBPs in late-stage clinical trials which will hopefully soon be authorized?

VCLS Answer: I do know there is one product being assessed by the FDA – it's an LBP. I do not know if there is a product being assessed by the EMA as these are confidential. There is one LBP close to approval in the US, which might be the first one as an LBP that might be put on the market. In EU we don't have that transparency or visibility due to the privacy around this type of products.

Clinical trials.gov provides information on clinical trials but perhaps not the intricacies of what studies are ongoing but we would just have the high-level information for clinical trials.

To conclude a lot of items we mentioned today are dealt with on a case-by-case basis to confirm and it is necessary to verify how it will apply to your product. These are general recommendations with key points of warning please consider that each product has its specifics and the way it will apply to your case and how you will have to involve the specific characteristics of development should still be verified on a case-by-case basis and ensure you are not missing anything as part of your development.

It's very important to interact with the authorities very early in development. You need to get an understanding how they view your product so it is important to apply

for a CAT classification right from the start. In terms of the CMC and quality aspects, we have mentioned that the monograph and the EUPharm provides the CMC perspective. For nonclinical you already have the ICH guidelines and if your product resembles an ATMP then use the guidelines on quality, nonclinical and clinical in Europe. If there is nothing in Europe, you can always leverage FDA guidelines in that case as they have a guideline on LBP.

It's crucial to interact with the regulatory agencies as early and frequently as necessary. If you are going for a clinical trial, then maybe you should liaise with them on a national level with the country where you want to conduct the trial. If you are in late phase, then maybe you want to get an agreement with the EMA at a more strategic level to get support to whatever it is you want to do.

If there is any ambiguity with the development please clarify with the agency, don't go ahead without asking whether they agree with the approach or not. Even if you ask for their advice and you decide not to follow their advice you must try to justify whatever position you take. Each product should be handled on a case-to-case basis. Please interact with the regulatory agencies they want to help you, it's not about being obstructive to developers, it's about making sure patient and subject health are protected at every stage of development.

Please see the regulatory agencies as your partner along your development journey, they are not just there to give you the green light on specific product, they are there to help you refine your strategy, providing advice and being a true partner for all developers.