Opportunity for Scottish Pharmaceutical Service Companies in Microbiome Drug Discovery and Development

Report 1

for

Scottish Enterprise

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1.0 Executive Summary

Globally there are at least 99 commercial organisations actively developing treatments based on microbiome-based approaches. The bulk of organisations are based in the USA (54). It should also be noted that research studies suggest that from an academic viewpoint, there are some 300 groups worldwide involved in earlier stages of discovery. These are likely to form a further pipeline of developments as research progresses via additional company formations or licence deals to players in the space.

In terms of therapy type classification, current developments at lead stages, as defined by the most advanced in each individual commercial organisation would suggest that single species of bacteria and consortia are the predominant classes at this point in time. The top areas of focus in terms of disease indications are Crohn's disease, Immuno-oncology, and C. Difficile infection. In terms of stage of development of the most advanced treatments cited, the bulk are at early stages. 42 at before human evaluation (Proof of concept or Preclinical), and 50 at early-stage human evaluation (Phase 1 or 2).

It should be noted that there are a number of organisations globally that are seeking to specifically provide services to microbiome therapy developers. 32 have been identified in this study.

At its crux the key challenge in the development of microbiome therapeutics is one of complexity. Ideally microbiome therapeutic discovery requires information on drugs, microbiota, and microbiota-human interactions. In this regard, large bioinformatic databases bringing this information together do not yet exist.

Currently identification of live bacterial therapeutic candidates usually occurs via a 'top down' approach, in which bacteria are selected based on the observation that they are enriched or reduced in individuals with disease or who are resistant to disease. Though this methodology has discovered potential therapeutics it gives little consideration for therapeutic mechanism, dose, or heterogeneity between individuals. This lack of knowledge creates significant issues during both preclinical and clinical stages of development.

One of the potential regulatory concerns is proving efficacy, because the composition of the microbiota is heavily dependent on the environment (including factors such as oxygen concentration, pH, acid and metabolites) and is therefore host specific. This can be a challenge during pre-clinical development, where non-clinical programmes must be carefully planned to account for the host-specific nature of microbiota in order to establish efficacy. In contrast, a bottom-up in silico approach could exploit quality bioinformatic techniques to identify mechanisms of bacterial action, and search for microbiota that fulfils these actions. Such algorithms will require to consider a multitude of factors before recommending a strain

or consortia, such as efficacy, bioavailability, risk of toxicity, ease of formulation, and scalability. Deep learning techniques, which can incorporate multiple layers of machine learning algorithms, would be well suited to solve these kinds of complex tasks.

Running in parallel with the need to improve informatic analysis is the need for model systems that allow the study of potential efficacy. This challenge applies to in vitro, ex vivo and animal model systems. For instance, most in vitro models do not reproduce the sessile state bacterial populations in the colon and do not reach the high bacterial density and microbial competition of the gut.

This is also the same challenge when using animal models of disease generated through human microbiome transplantation. Genetic, physiological, and anatomical differences between humans and animals affect engraftment, naturally favouring those microbiome phylotypes best adapted to survive in the new host.

In Scotland there are 65 organisations that can be classed as capable of offering Pharma services and tools. The majority of which are associated with clinical trials. It is fair to state at this point that there is not a strong focus on supporting Microbiome based treatment development. This is to be expected given the fact that this area is emerging and has not been a focus in Scotland to date. From an actual therapy development viewpoint only Enterobiotix is active within the region. However, it is important to note that many of the skills/assets and knowledge gained in the development of small molecule and Biologic based drug discovery and development are transferrable to Microbiome based approaches. Assessment of organisations within the Scottish Ecosystem suggests that 8 organisations offer aspects of microbiome treatment development support.

The market is significant from a valuation perspective, and it is estimated that the outsourced pharma services can be valued at $409,600,000 in 2021, rising to $1,774,780,435 by 2026, and $7,958,174,813 by 2031. From a geographic perspective the USA is the largest market at 55%, followed by Europe at 30%.

We offer two recommendations for consideration:

1. Contact with the endogenous service sector to understand awareness of the microbiome opportunities and possible plans to engage and support needed

2. More research in the form of Voice of Customer engagement is required as to precise requirements desired by companies developing therapeutics. Identification of unmet needs and or areas of dissatisfaction with current outsource service provision.

2.0 Methodology

The methodology used is desktop research and analyses, data sources are highlighted.

Objective	Datasource/Methodology
Map out the current European and US discovery and development pathway for novel LBPs and other relevant therapeutic modalities for targeting the microbiome (excluding biologics and small molecules).	• **Discovery** – Research Publications 2011 to 2021 (Science Direct/Goggle Scholar/ Scopus/Web of Science/PubMed) • **Development** – FDA, EMA & MHRA published data and advisory dockets
Identify key global players in the field of microbiome therapeutic discovery and development. This should include pharma/biotech companies developing microbiome-targeted therapeutics but also CRO/CMO/CDMOs and suppliers with key capabilities in this space.	• Market Research Reports • Company Announcements • Pitchbook Investment • Trials ongoing cited by ClinicalTrials.Gov • European Patent Office • Trade Literature • Key Microbiome Meetings
Provide an overview of potential gaps and opportunities in the supply chain for development of new therapeutics targeting the microbiome and include, based on awareness of Scottish company capability, an assessment as to Scotland's readiness/ability to capitalise on the opportunity, highlighting key Scottish companies (particularly SMEs)	• Review of the assets of organisations listed in the Scottish Life and Chemical Science Directory • Published referenceable issues reported in the literature. • Map of assets to reported issues
Recommend further work that may be required to fully understand/develop opportunities	• Scottish Assets Gap and Close analysis
Value chain analysis	• Value chain market value analysis

Table 1: Client Objectives and match to Methodology

3.0 The discovery and development pathways for novel therapeutic approaches to targeting the microbiome

Microbiome drug developers are using many different therapeutic strategies which may be summarised as follows:

Faecal microbiota transplantation (FMT) - Historical records cite that FMT was first described in the 4th Century in China, the method has increased in practice since the 1950's primarily to the ability to ameliorate collateral damage on commensal microbe within the gut post antibiotic therapy[1,2]. Technically FMT involves the transfer of processed faecal microbiome material from a healthy donor to a diseased individual. From a commercial development point of view different regulatory, IP and safety[3-5] considerations have made it less attractive to the mainstream pharmaceutical industry.

Defined consortia

This approach is based on treating the patient with a consortium of several live bacterial product (LBP) microbial species (usually between two to twelve). From a discovery point of view, some of these potential treatments have emerged from further processing and refinement of FMT. Others have been designed rationally focussing on ecological properties, metabolic capacities, or other features that have been found via basic and applied research.

Single species (strain)

In this strategy, a single type of microorganism is administered to cause the favourable result desired. This popular approach is used by many developers. Most of the programs in this cluster are exploiting the targeted crosstalk between a specific bacterial strain and the immune system to aim at treating inflammatory diseases and cancer.

Phages

The human 'phageome' which encompasses the collection of viruses targeting the bacterial microbiome within the human body, is being increasingly recognised as an important factor in microbiome composition and dynamics. The most discernible application of bacteria-killing viruses is combating infectious disease, and this is where most of the phage projects are being researched. However, new applications like oncology and inflammatory diseases are also emerging within this area.

Genetically modified organisms (GMOs)

The metabolic capabilities of microorganisms are almost limitless and not yet fully described[6]. Some companies are engineering microbes to turn them into long-term drug delivery systems, or to expand or potentiate their endogenous metabolic activity. The microbiome produces tens of thousands of different, chemically diverse substances, most of them yet unknown to man[6]. Many have been demonstrated to have significant physiological effects[7-9] and therefore may have huge pharmacological potential[10,11].

Small molecules

In this context small molecules are novel synthesised organic compounds with a low molecular weight with unique chemical structures not naturally found in nature. They are often termed as new molecular entities (NMEs). Such developments are the basis for the bulk of traditional drug discovery and development. This is due to the fact that as NMEs are not found in nature, they can be readily patented forming an effective barrier to competitive developments.

Natural Products

In this context, these are products of bacterial metabolism that have a potential therapeutic benefit. In contrast to small molecules natural products are found in nature. This approach is not favoured by mainstream pharmaceutical industry due to the challenges in IP development.

3.1 Clinical Developments

As of March 2022, globally there are at least 99 commercial organisations actively developing treatments based on microbiome-based approaches.

The bulk of organisations are based in the USA. This concentration is a consequence of investment availability within the USA with $1.6 Billion being invested over the last two years. Overall US investment levels are estimated to be in the region of $4B since 2010. Financial support in Europe has been less and unreported to a large extent. The recent announcement on the 7th of March 2022, that Microbiotica, a UK based player had received a $67 million Series B financing round is indicative that the area is also attractive in Europe. This is the largest microbiome-related financing in Europe to date.

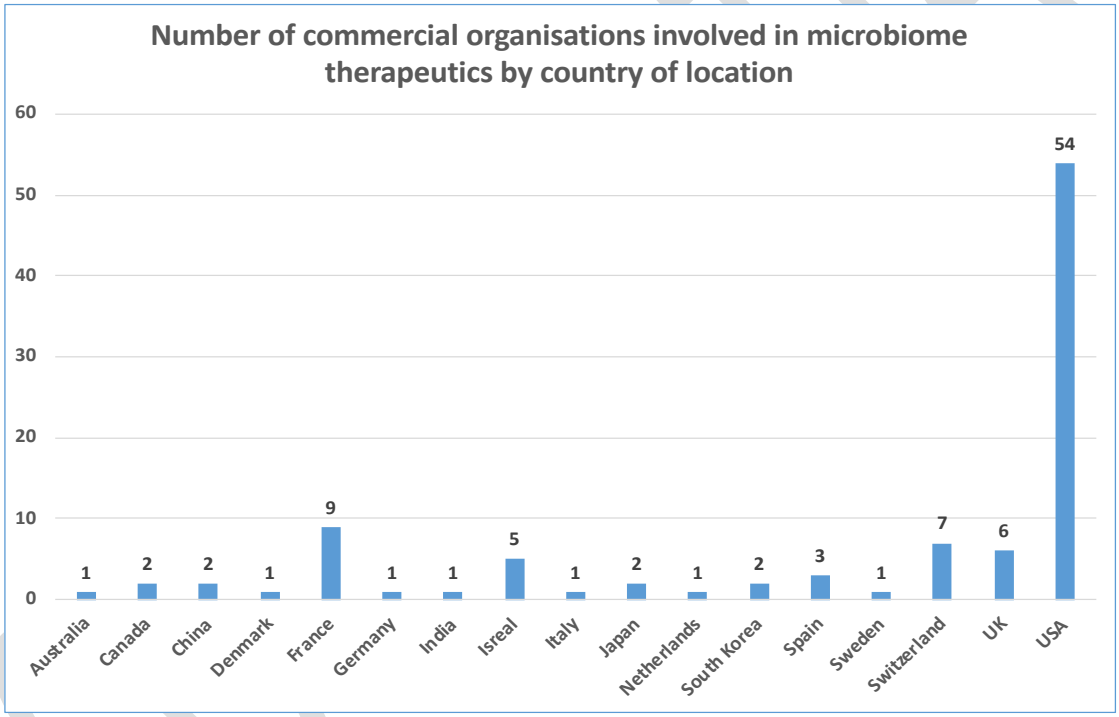

Figure 1: Commercial Microbiome players as of March 2022 (Datasource: Analysis of Company/Industry announcements)

It should also be noted that research studies suggest that from an academic viewpoint, there are some 300 groups worldwide involved in earlier stages of discovery.

These are likely to form a further pipeline of developments as research progresses via additional company formations or licence deals to players in the space. For more detail on the organisations identified please refer to Appendix 1. It should be noted that commercial company formation has increase annually over the last 10 years (see Figure 2). Dates of foundation could not be found for two of the Chinese organisations.

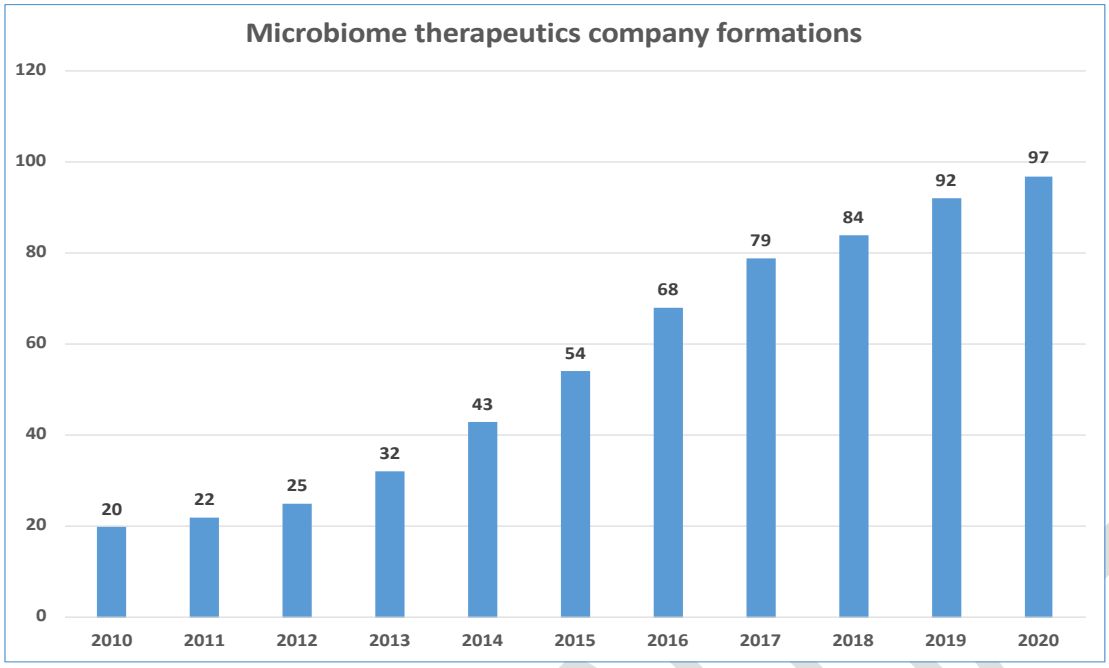

Figure 2: Growth in Microbiome company formations 2010 to 2020 ((Datasource: Analysis of regional companies' house data)

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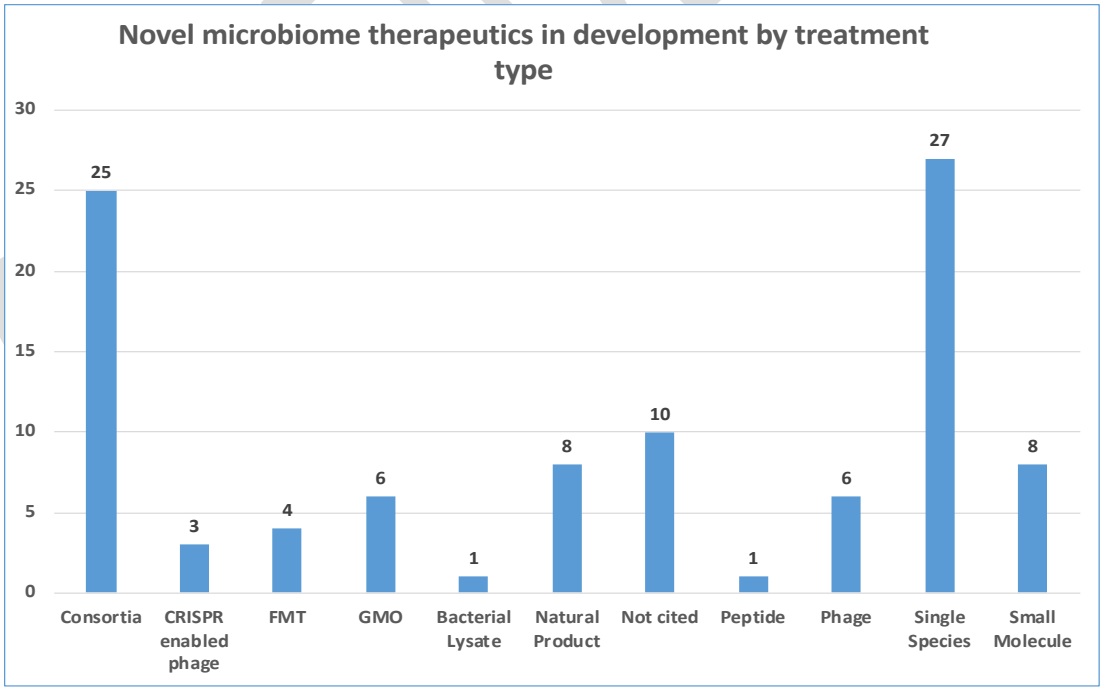

Figure 3: Commercial Microbiome players by Treatment Type (Datasource: Analysis of Company announcements)

The top areas of focus in terms of disease indications are Crohn's disease, Immuno-oncology, and C. Difficile infection.

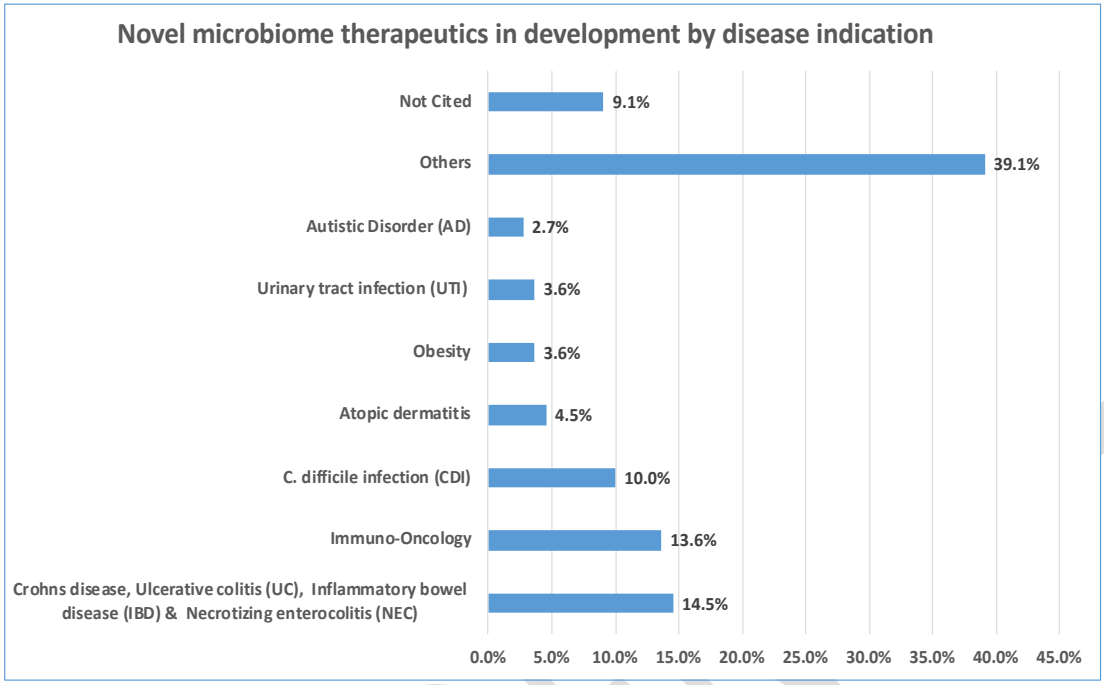

Figure 4: Commercial Microbiome players by Treatment Type (Datasource: Analysis of Company announcements)

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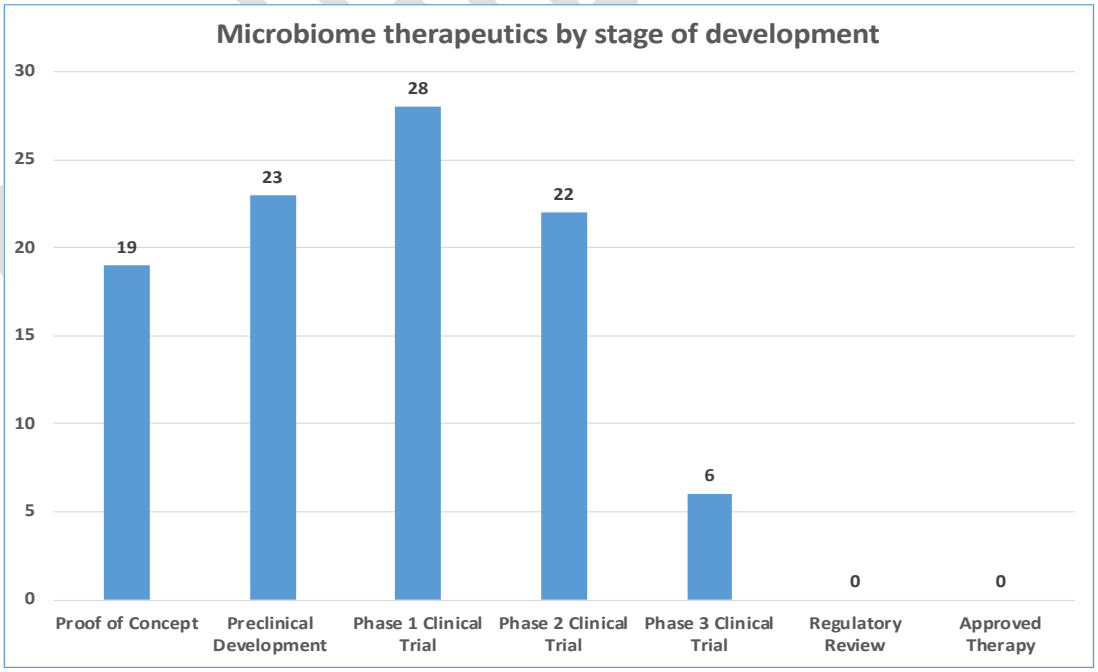

Figure 5: Commercial Microbiome players by Lead treatment stage of Development (Datasource: Analysis of Company announcements)

3.2 Current Microbiome Pharma Services

It should be noted that there are a number of organisations globally that are seeking to specifically provide services to microbiome therapy developers. 32 have been identified in this study. These organisations in terms of services can be segmented as follows:

Category	Commentary
Bacterial Strain Supply	Provision of characterised single strains or consortia
Microbiome sequencing and bioinformatic analysis	Next generation sequence analysis of strains and associated genetic information analysis
Disease models	Models of disease
GMO	Capabilities to create novel genetically modified organisations
CDMO	Full-service provider offers scale up development and QC/QA
Others	Formulation, packaging, and tools for stool recovery for analysis

Table 2: Current Microbiome Pharma Services

From a regional perspective the USA as would be expected given the level of development activity has the largest number of such organisations.

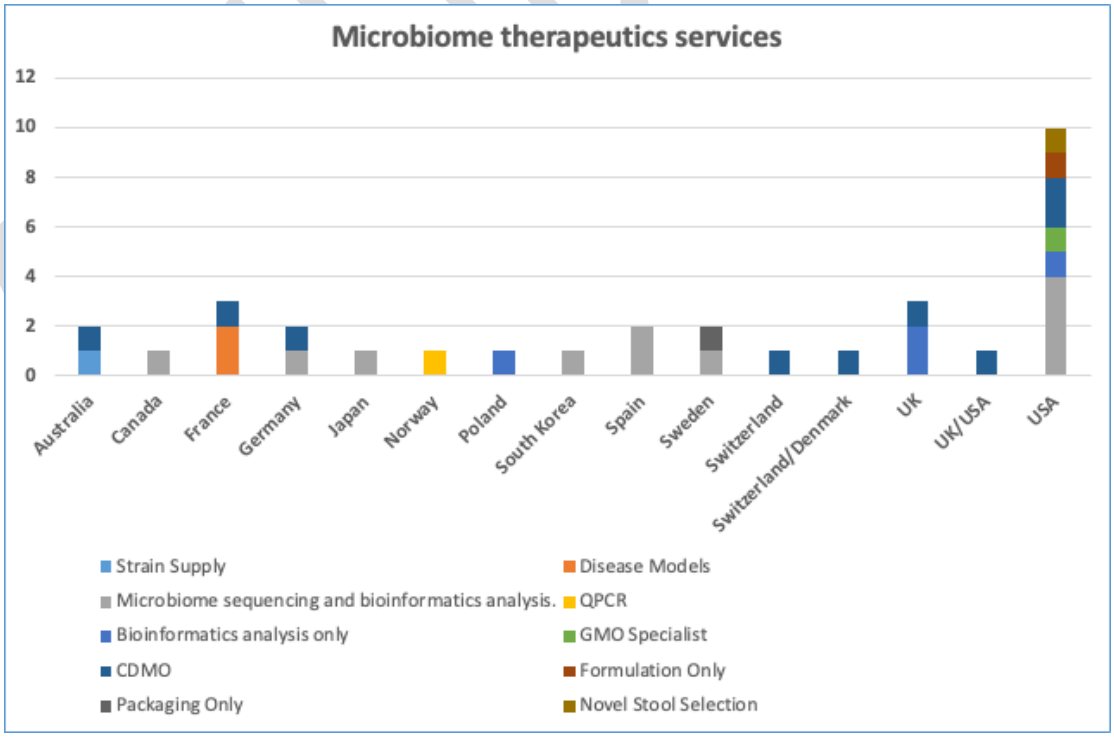

Figure 6: Location of Microbiome Pharma Service organisations by category of offerings (Datasource: Analysis of Company announcements)

For more details on these service organisations please refer to Appendix 2.

4.0 Summary of the challenges and potential opportunities in this area

At its crux the key challenge in the development of microbiome therapeutics is one of complexity. The human microbiome involves trillions of microorganisms that live on and within the human body. Members of the microbiota include bacteria, viruses, fungi, archaea, and protozoa. Collectively they inhabit nearly every region of their human host[12].

Bacteria alone encode for over 100-fold more unique genes than humans[13]. Subsequently, microbiota is known to exert extensive influence upon human health and metabolism. For example, the development of metabolic syndrome a medical term for a combination of diabetes, high blood pressure (hypertension) and obesity. Others include Parkinson's disease, inflammatory bowel disease, and periodontitis which are strongly associated with imbalanced, also known as 'dysbiotic', microbiome compositions[14-18].

Endogenous moieties that are broken down by microbiota include bile acids, hormones, and intestinal mucus[19]. Drugs are also highly susceptible to metabolism by microbiota. A seminal study found that of 271 commonly administered oral drugs, 176 (64.9%) of them were significantly metabolised by at least one strain of 76 human gut bacteria[20]. Due to substantial differences between individuals' microbiomes, drug metabolism by microbiota can result in significant interpatient variability in pharmacokinetics and pharmacodynamics[21]. The consequence of which at its extreme is a portion of the patient population that are in effect resistant to treatment.

Whilst the microbiome can impact the actions of drugs, the same applies in converse. Studies have highlighted that a significant proportion of non-antibiotic drugs impair growth of gastrointestinal microbiota[22].

From the beginning of the 21st century, microbiome-based research has amassed at an increasing rate. In the mid-2000s, the impact of affordable and accurate DNA sequencing methods facilitated the commencement of the Human Microbiome Project: a multi-site collaboration leading to the genomic profiling of microbiota at key body sites[23].

Later, the project assessed the role of the microbiome in human health and disease[24]. In parallel to this field leading work, many other laboratories worldwide have contributed to the now extensive knowledge base concerning the microbiome. Vast quantities of data have been made globally accessible through publications and online databases, such as the NIH Human Microbiome Project Data Portal; MicrobiomeDB; and China National GeneBank[25-27]. Such data are being increasingly utilised by scientists to design microbiome targeted therapies and predict microbiome-drug interactions.

Ideally microbiome therapeutic discovery requires information on drugs, microbiota, and microbiota-human interactions. In this regard, large databases bringing this information together do not yet exist, therefore at this point in time it is necessary to mine and analyse data from multiple sources.

Currently identification of live bacterial therapeutic candidates usually occurs via a 'top down' approach, in which bacteria are selected based on the observation that they are enriched or reduced in individuals with disease or who are resistant to disease[28].

Though this methodology has discovered potential therapeutics it gives little consideration for therapeutic mechanism, dose, or heterogeneity between individuals[29,30]. This lack of knowledge creates significant issues during both preclinical and clinical stages of development.

In contrast, a bottom-up in silico approach could exploit quality bioinformatic techniques to identify mechanisms of bacterial action, and search for microbiota that fulfils these actions. Such algorithms will require to consider a multitude of factors before recommending a strain or consortia, such as efficacy, bioavailability, risk of toxicity, ease of formulation, and scalability. Deep learning techniques, which can incorporate multiple layers of machine learning algorithms, would be well suited to solve these kinds of complex tasks.

Running in parallel with the need to improve informatic analysis is the need for model systems that allow the study of potential efficacy. This challenge applies to in vitro, ex vivo and animal models systems.

For instance, most in vitro models do not reproduce the sessile state bacterial populations in the colon and do not reach the high bacterial density and microbial competition of the gut.

For instance, the most common model currently used is the so-called Simulator of the Human Intestinal Microbial Ecosystem (SHIME). The SHIME is an array of culture vessels that seeks to mimic the entire gastrointestinal tract incorporating stomach, small intestine, and different colon regions. The microbiota used is usually derived from a single donor faecal microbiome sample.

A recent approach to solve these sessile state limitations has been developed, the PolyFermS system, which includes a process of immobilisation of faecal microbiota in gel beads mimicking cell density and competition of in vivo gut microbiota. PolyFermS gut models can be expanded to various configurations including infant, elderly, or obese donors, allowing for a comparison of a control with different treatment effects with the same microbiota, ideal for investigating mechanisms of action and bacterial metabolite profiles of multiple prebiotics.

An important disadvantage of this set-up is the lack of mechanisms for short chain fatty acids (SCFA) absorption. SCFA are products of bacterial metabolism, 95% of these acids are estimated to be rapidly absorbed by the colonic epithelium. Therefore, models such as PolyFermS are operating under a condition where there is a continuous build-up of SCFA in the culture which is not the case in vivo due to the absorption effect.

Ex vivo studies are often carried out using pig intestine which shows a high degree of macroscopic and microscopic resemblance with that of humans and is considered the best alternative for human tissue. However porcine ex vivo intestinal segment models do not reflect the same microbiota as that of humans.

This is also the same challenge when using animal models of disease generated through human microbiome transplantation. Genetic, physiological, and anatomical differences between humans and animals affect engraftment, naturally favouring those microbiome phylotypes best adapted to survive in the new host. More importantly, the host's immune system, which lies at the host-microbiome interface and channels signals from the microbiome to direct the host's response to environmental cues and to, in turn, regulate the microbiome composition and dynamics by the host, varies greatly among species.

Human microbiomes have been transplanted into both conventionally raised animals and germ-free animals. With conventionally raised animals, the purpose is to displace and hopefully replace the host's microbiome with the transplanted human microbiome in a 'natural and gradual' way. With germ-free animals, the goal is to create germ-free (gnotobiotic) animals displaying the human microbiome only.

In both instances, however, the transplanted human microbiome needs to adapt to a set of host-specific physiological and topological niches and an immune system it has not co-evolved with, and it needs to engraft in an environment where the host's immune system has not developed from birth with a human microbiome, or any microbiome in the case of germ-free animals.

Efforts to overcome these challenges include the use of animals with humanised immune systems, and to perform experiments on the offspring of transplanted parental animals that would have co-developed their immune systems with the transplanted.

Beyond co-evolution and co-development, physiological and topological niche disparities could further be addressed by moving up from rodents, on the evolutionary scale, and to enlist non-primate animal models such as pigs or even non-human primates with immune systems, physiologies, and anatomical characteristics closer to humans. Practically, however, such efforts are hampered by the complexity and expense of performing experiments with large animals.

But despite all these approximations, it will remain challenging to determine whether a dysbiotic state recreated in any animal model is truly representative of the human pathology.

In addition to the discovery challenges, depending on the nature of the treatment, manufacturing is also multifaceted. For live biotherapeutics, because of the complexity of the product, there is a potential for change to occur between batches over time if not properly controlled. This problem is multiplied exponentially if the product contains multiple organisms.

As with all novel therapeutic modalities, the regulatory side that developers come across is a challenge. In the US, LBPs are typically handled by the FDA's vaccines division, while in Europe, the EMA treats them generally as biologics. Yet LBPs often have their own specific requirements, and require special considerations for quality, safety, and efficacy documentation before being used in humans. For example, LBPs must be assessed for potential antimicrobial resistance genes and evaluated to ensure they do not cause sepsis or infection. Such evaluations that are not necessarily required with products such as vaccines or antibodies. The FDA defined pharmaceutical expectations for LBPs in 2012 (updated in 2016) and the European Pharmacopoeia (Ph. Eur.) established their quality requirements in 2019. One paper asserted that one of the remaining challenges is that, since LBPs are yet to be approved for the market, the guidance lacks explanations of exactly how drug regulatory requirements should be addressed in practice.

One of the potential regulatory concerns is proving efficacy, because the composition of the microbiota is heavily dependent on the environment (including factors such as oxygen concentration, pH, acid and metabolites) and is therefore host specific.

If an LBP is designed to impact on the microbiota for its effects, these may differ in different hosts. This can be a challenge during pre-clinical development, where non-clinical programmes must be carefully planned to account for the host-specific nature of microbiota in order to establish efficacy.

In summary the regulatory requirements in the USA and Europe can be summarised as follows:

Required information	Methodology
Genotyping • Identification at species level • Identification at strain level • Antimicrobial resistance genes • Virulence genes • Presence of mobile genetic elements • Plasmid detection Bacteriophage-related DNA insertions • Transposons	• 16S rDNA genotyping • Whole genome sequencing • Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF)
Phenotyping	
Morphology identification Gram staining Cell shape and size	• Microscopy
Growth characteristics	• Growth kinetics, pH tolerance, aerotolerance, bile acid resistance
Motility and sporulation	• Wirtz-Conklin method
Antibiotic sensitivity profile	• Antibiogram demonstrating minimum inhibitory concentrations
Enzymatic activity	• API 20A anaerobic test, API rapid ID32A, API ZYM, oxidase, and catalase activity
Bacterial endotoxins	• Method A: gel-clot technique Method B: turbidimetric technique • Method C: chromogenic technique

Table 3: Microbiome FDA/EMA Regulatory requirements

It should be noted that the EMA has specified that the whole genome sequence of the strain must be included in the final product's dossier, as well as the detailed list of the identified antibiotic resistance genes, multidrug resistance clusters, putative virulence factor genes, only the FDA provide details regarding the quality of the genome sequencing and associated bioinformatic analysis.

5.0 Scotland's Pharmaceutical Services sub-sector's readiness/ability to capitalise on the opportunities

In Scotland there are 65 organisations that can be classed as capable of offering Pharma services. The majority of which are associated with clinical trials.

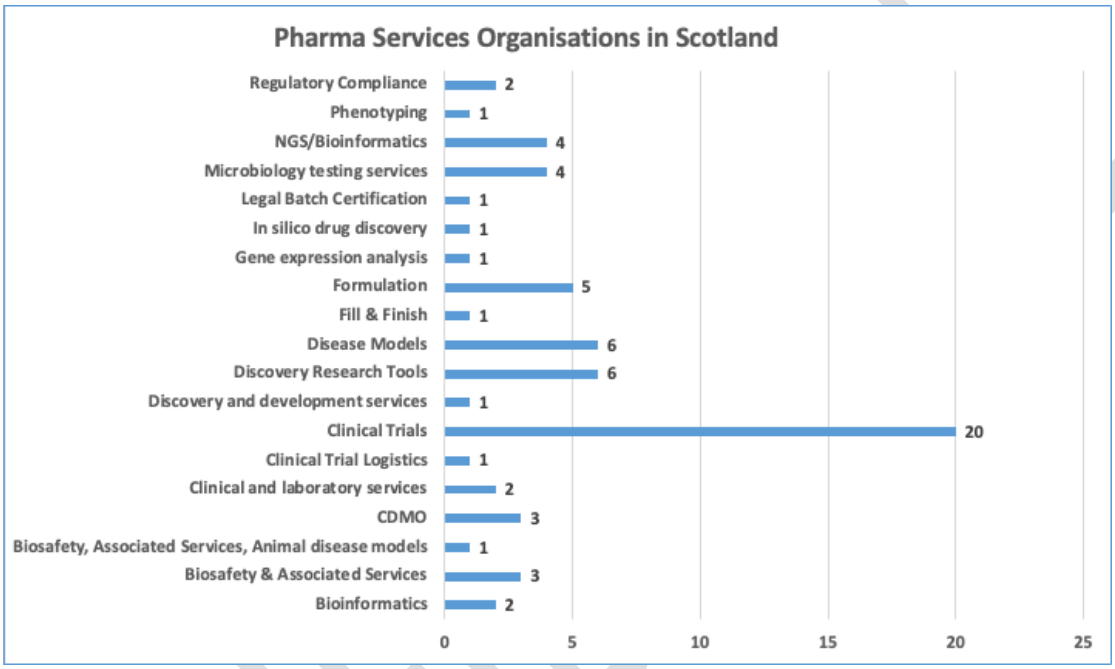

Figure 7: Scottish Pharma Service organisations by category of assets/offerings

For more detail on these organisations please refer to Appendix 3.

It is fair to state at this point that there is not a strong focus on supporting Microbiome based treatment development. This is to be expected given the fact that this area is emerging and has not been a focus in Scotland to date. From an actual therapy development viewpoint only Enterobiotix is active within the region.

However, it is important to note that many of the skills/assets and knowledge gained in the development of small molecule and Biologic based drug discovery and development are transferrable to Microbiome based approaches.

Assessment of organisations within the Scottish Ecosystem suggests that 8 organisations offer aspects of microbiome treatment development support.

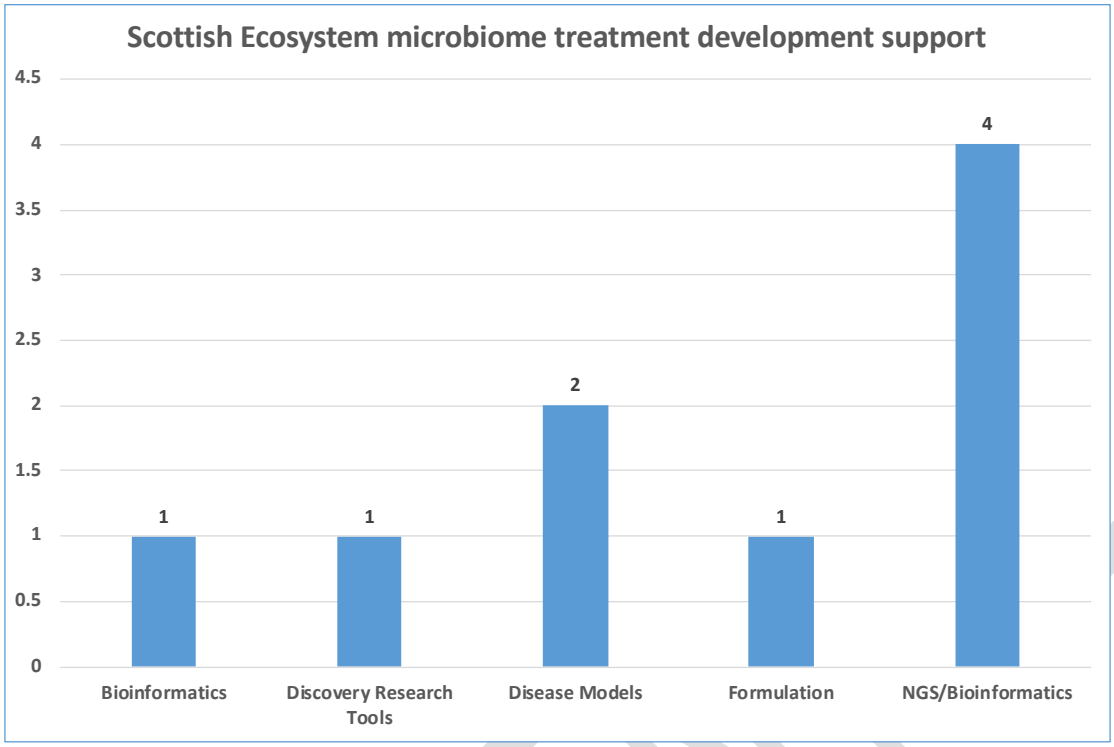

Figure 8: Scottish based organisations that offer microbiome discovery and development services by service category

Future potential opportunities for Scottish pharma service companies include key aspects such as biosafety and associated services, CDMO provision and clinical trial support.

6.0 Value chain market value analysis

Assessing the value of the market for outsource services to aid in microbiome therapeutics is a challenging process. This is since the field is emerging with no actual costs reported at the various stages of development. The following assumption-based model is intended to provide an indication of the likely value in 2021, 2026 and by 2031. The valuation is based on the latest data on the costs for pharmaceutical development that cites values for different types of treatments[31], which builds on the work of others in the field such as DiMasi[32-34]. The advantage of this analysis is the fact that development costs are segmented according to types of treatments. In the valuation presented the costs for complex biologics have been used. The costs have been presented on an annual basis taking into account the fact that total costs are incurred over time. The numbers in development (Proof of concept to Phase 3) are those found in Figure 5: Commercial Microbiome players by Lead treatment stage of Development.

	Total Costs	Timescale (Years)	Annual Costs	Numbers in development
Proof of Concept	$3,500,000	5	$700,000	19
Preclinical	$16,600,000	3	$5,533,333	23
Phase 1	$2,500,000	2	$1,250,000	28
Phase 2	$13,900,000	2	$6,950,000	22
Phase 3	$126,000,000	3	$42,000,000	6

Table 4: Valuation assumptions used to calculate Market

To model the values over the next ten years, an annualised growth rate has been applied 35%. This is the growth rate in new companies being formed in this area. The valuation assumes 60% of development activities are likely to be outsourced similar to other types of pharmaceutical development.

60% Outsourced Model	Year		
Service Segment	**2021**	**2026**	**2031**
Discovery (5 years)	$48,300,000	$154,699,154	$693,676,177
Preclinical (3 years)	$76,360,000	$342,400,793	$1,535,336,606
Phase 1 (1 year)	$42,000,000	$188,329,404	$844,475,346
Phase 2 (2 year)	$91,740,000	$411,365,228	$1,844,575,435
Phase 3 (3 years)	$151,200,000	$677,985,856	$3,040,111,247
Total	**$409,600,000**	**$1,774,780,435**	**$7,958,174,813**

Table 5: Valuation Model 2021 to 2031

It should be noted that the valuation cited in Table 7 is the global value. From a geographic perspective the USA is the largest market at 55%, followed by Europe at 30%.

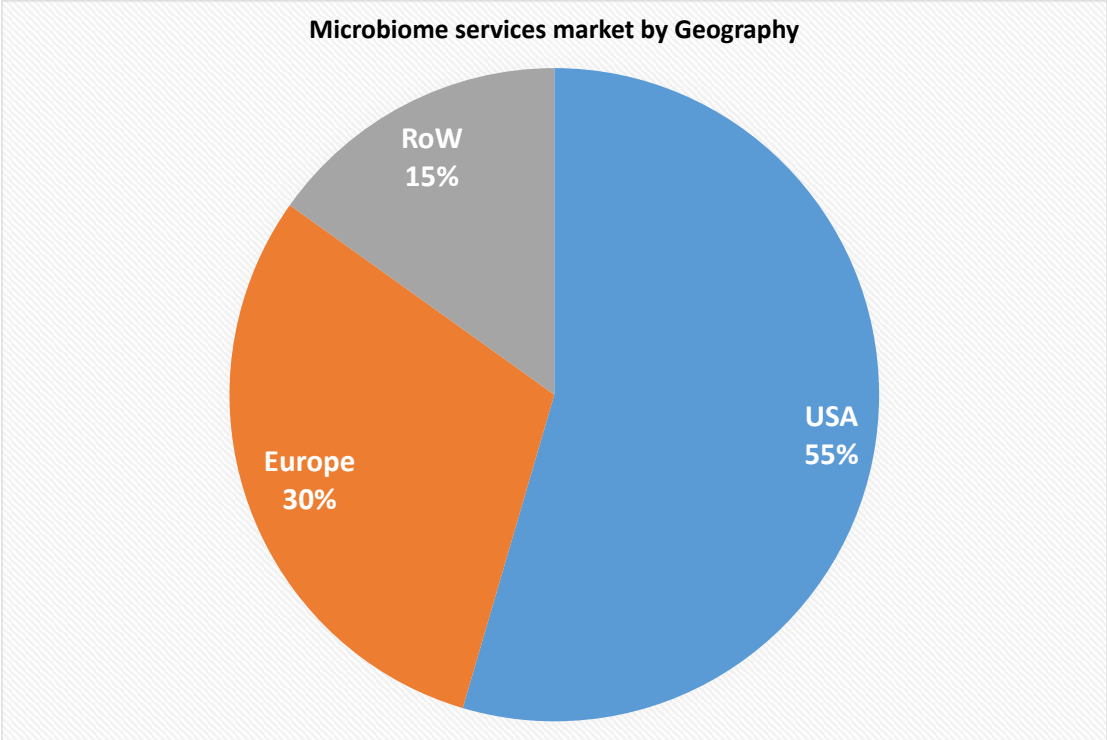

Figure 9: Microbiome services market by Geography.

7.0 Conclusion/Discussion

There is no doubt that the Microbiome therapeutic sector is experiencing a growth in developments. What differentiates this emerging market compared to others that have appeared over the years such as cell therapy is the level of early-stage major pharma engagement.

This fact makes the sector extremely attractive to the Venture capital community who perceive the potential for early-stage exit than is usually possible in pharmaceutical drug discovery and development.

Notable deals and collaborations include:

Date - Microbiome Co./Partnering Co.	Summary
Dec 2021 - Kaleido Biosciences/Jansen	Expansion of collaboration to explore potential of Microbiome Metabolic therapies (MMT™) to prevent childhood-onset of Atopic, Immune and Metabolic Conditions.
July 2021 - Seres/Nestle	Nestlé has agreed to pay $175 million up front, another $125 million upon Food and Drug Administration approval, and as much as $225 million if certain sales goals are met.
June 2021 - SNIPR Biome/Novo Nordisk	Research agreement on an undisclosed target
Jan 2021 - Vedanta/Pfizer	$25 million investment in Vedanta
Jan 2021 - Eligo Bioscience/GSK	Research and option agreement, eligible to receive up to a total of $224 million in license fees and potential milestone payments, as well as royalties on global sales.
Sept 2020 - BiomX/Boehringer	Collaboration to potentially identify biomarkers associated with patient phenotypes in inflammatory bowel disease (IBD)
June 2020 - Debiopharm/Takeda	Partnership to develop microbiome therapeutics to treat IBD and other GI disorders.
Apr 2020 - Second Genome/Gilead	Partnership to identify biomarkers for five of Gilead's clinical candidates and drug targets for IBD. Second Genome will receive $38 million upfront.
Nov 2019 - Finch Therapeutics/Takeda	Expands its partnership to develop microbiome-based therapeutics using Finch's Human-First Discovery platform.
Oct 2019 - 4D Pharma/ Merck & Co	Research deal to develop live biotherapeutics for vaccines. 4D will receive up to $347.5 million in milestone payments as well as an upfront cash payment.
Mar 2019 - Seres /AstraZeneca	Partnership to evaluate microbiome-based therapies on their capacity to augment cancer immunotherapy.
Nov 2018 - Vedanta Biosciences/Janssen	Deal to commence phase 1 study of VE2020 for IBD. Through the deal Vedanta will receive up to $12 million in ongoing milestone payments'
Oct 2018 - Enterome/Takeda	licensing and co-development deal—including $50 million up front and up to $640 million in milestones with Takeda—for the development of EB8018 for Crohn's disease.
June 2018 - Microbiotica/Genentech	Microbiotica signs $534 million deal with Genentech to develop biomarkers, targets and therapeutics for IBD using its precision metagenomics microbiome platform.
April 2018 - Rebiotix/ Ferring Pharmaceuticals	Ferring Pharmaceuticals acquires Rebiotix and its microbiota restoration therapy platform and lead candidate RBX-2260 in development for Clostridium difficile infection.

Table 6: Mainstream Pharma engagement in Microbiome Therapeutics

It can't be stressed just how unusual this situation is, the mainstream pharmaceutical industry is often risk averse with regards to novel therapeutic approaches. In terms of companies active in development globally 99 have been identified. This number is likely to increase significantly driven by the mainstream pharma interest and availability of venture capital.

In terms of outsource provision, globally there is the beginning of a cluster of organisations that are dedicated to offering value added services to support discovery and subsequent development. In terms of Scottish based organisations, it is fair to state that to date there has been little move in this direction. This is likely to be a consequence of lack of awareness, and or the perception that the cost to enter and required assets are prohibitive.

8.0 Recommendations for further work to fully understand/develop particular opportunities for Scottish pharma service companies to increase exports in the microbiome therapeutic spaces

We offer two recommendations for consideration:

1. Contact with the endogenous service sector to understand awareness of the microbiome opportunities and possible plans to engage and support needed

2. More research in the form of Voice of Customer engagement is required as to precise requirements desired by companies developing therapeutics. Identification of unmet needs and or areas of dissatisfaction with current outsource service provision.

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Appendix 1 – Microbiome Therapy Developers

Organisation	Location(s)	Lead Development Science	Class	Disease Indication
Servatus Ltd	Australia	Live Microbial Biotherapeutics (LMB)	GMO	Chronic Idiopathic Constipation (CIC) / IBS-C
MedBiome	Canada	Berberine (BBR) and 16 structural analogs	Natural Product	Not cited
NuBiyota	Canada	Multi-strain microbiome therapeutic composition candidates	Consortia	Hypertriglyceridemia (HTG); Depression, Anxiety
Chaozhou enterprise Guangdong Longchuangji Pharmaceutical Co., Ltd	China	Lactobacillus rhamnosus	Single Species	Bacterial Vaginosis
Zhiyi Pharmaceutics	China	SK08 Bacteroides fragilis	Single Species	Irritable bowel syndrome (IBS)
SNIPR BIOME ApS	Denmark	Oral medication that contains four E. coli-targeting Phages. Intended to deliver its CRISPR reagents as CRISPR-Guided Vectors™ (CGV™ Technology) into target bacterial cells. Once inside target cells, CGVs assemble into Cas-RNA complexes that create double-stranded breaks in bacterial genomes, leading to ultra-rapid killing in a matter of minutes, allowing rapid response in acute settings.	CRISPR enabled phage	Escherichia coli infections in haematological cancer patients

Organisation	Location(s)	Lead Development Science	Class	Disease Indication
Eligo Bioscience SA	France	EB003, Eligo's lead drug candidate, was developed using the Company's proprietary Sequence-Specific Anti-Microbials (SSAM) platform. SSAM relies on the delivery of a non-replicative DNA payload encoding an exogenous Cas nuclease, guided towards specific genomic sequences. This modality leads to targeted lethal DNA double strand-breaks only if such sequences are present in the bacterial genome.	CRISPR enabled phage	Severe diarrhoea induced by shiga-toxin (Stx) producing E. coli (STEC, leading to Haemolytic Uremic Syndrome)
Enterome	France	Sibofimloc binds FimH, a novel microbiome-derived therapeutic target validated by Enterome, to selectively disarm virulent bacteria in the gut that can cause intestinal inflammation without disrupting the local microbiome.	Small Molecule	Crohn's Disease
EverImmune	France	Developing Oncobax® AM as an immunogenic commensal bacterium in combination with ICBs for the treatment of non-small cell lung cancer (NSCLC) patients. The lead candidate is a specific strain of Akkermansia muciniphila aiming to boost the efficacy of anticancer treatments significantly and safely.	Single Species	Non-small cell lung cancer (NSCLC)

Organisation	Location(s)	Lead Development Science	Class	Disease Indication
Exeliom Biosciences	France	EXL01 - Single Strain Faecalibacterium praustnizii	Single Species	Crohns disease
MaaT Pharma	France	MaaT013 is a donor-derived, standardized, high-richness, high-diversity microbiome ecosystem therapy, containing ButycoreTM , a group of bacterial species known to produce anti-inflammatory short-chain-fatty acids.	Consortia	Acute Graft-vs-host-Disease
NexBiome	France	Live Biotherapeutic Microorganism	Single Species	H.Pylori infections
SAS TargEDys	France	Commensal Hafnia alvei strain	Single Species	Obesity
Targedys	France	Hafnia alvei HA4597™ is one of the strains responsible for the typical “French” cheese taste and smell. Hafnia alvei HA4597® produces ClpB, a protein that acts through molecular mimicry of the satiety hormone alpha-MSH and regulates appetite.	Single Species	Obesity
YSOPIA Bioscience	France	Single Strain Christensenella minuta	Single Species	Metabolically unhealthy obesity
Conaris Research Institute	Germany	CR12/02 - Drug candidate: gut microbiota modulator (small molecule)	Small Molecule	Not cited
Leucine Rich Bio	India	LRB120305 is formulations for specific diseases	Not cited	Not cited
Biomica	Israel	BMC128: rationally-designed live biotherapeutic products (LBP) consortia comprised of unique bacterial strain	Consortia	Non-small cell lung cancer (NSCLC)

Organisation	Location(s)	Lead Development Science	Class	Disease Indication
BiomX	Israel	BX004 - BOLT (BacteriOphage Lead to Treatment) platform that uses phages — viruses, or a virus cocktail, that can infect and kill bacterial cells — instead of antibiotics as bacteria-targeting therapies. BOLT was designed to rapidly develop phages (within six to eight weeks) targeting specific bacteria in a manner tailored to a given patient.	Phage	Cystic Fibrosis
Ella Therapeutics	Israel	Fecal Microbiota Transplantation (FMT)	FMT	Metastatic Melanoma or NSCLC
MyBiotics Pharma	Israel	Donor Consortium of live bacteria	Consortia	C. difficile infection (CDI)
Wild Biotech	Isreal	Has created a database of more than 1,200 gut bacteria, about 75% of which were previously unknown. Intends to develop novel drugs based on gut bacteria from diverse species	Not cited	Not cited
Leadiant Biosciences Inc	Italy	STP-206 (lactobacillus acidophilus and Bifidobacterium animalis subsp. lactis),	Consortia	Necrotizing Enterocolitis/Neonatology
Miyarisan Pharmaceutical Co., Ltd	Japan	Clostridium butyricum MIYAIRI strain	Single Species	Antibiotic-Induced Dysbiosis
Takeda (License Nubiyota)	Japan	TAK 039 an orally administered bacterial consortium	Consortia	C. difficile infection (CDI)
Caelus Health	Netherlands	Lead product - E. hallii	Single Species	Diabetes
Genome and Company	South Korea	GEN-001 is a single-strain bacterium isolated from healthy humans	Single Species	Solid Tumors Immuno-oncolgy

Organisation	Location(s)	Lead Development Science	Class	Disease Indication
KoBioLabs Inc	South Korea	Lactobacillus gasseri KBL697 strain	Single Species	Inflammatory bowel disease (IBD)
Microviable Therapeutics	Spain	MVT-Prj-601 - Live biotherapeutic products (LBPs) based on rationally designed microbial communities.	Consortia	Atopic dermatitis
Mikrobiomik	Spain	Faecal Microbiome Transfer (FMT)	FMT	C. difficile infection (CDI)
Pulmobio	Spain	Genetically modified the lung pathogen Mycoplasma pneumoniae	GMO	Ventilator-associated pneumonia (VAP)
Infant Bacterial Therapeutics AB	Sweden	IBP-9414 contains the active compound Lactobacillus reuteri, which is a human bacterial strain naturally present in breast milk.	Single Species	Necrotizing enterocolitis (NEC)
Aurealis Therapeutics AG	Switzerland	AUP 16 - genetically engineered Lactococcus lactis	GMO	Diabetic foot ulcer (DFU)
Debiopharm	Switzerland	Debio 1454 is a FabI inhibitor targeting a combination of enteric bacteria species, A. baumannii, Enterobacter Spp., Klebsiella pneumoniae and E.coli.	Consortia	Inflammatory bowel disease (IBD) and other gastrointestinal (GI) disorders.
MV BioTherapeutics	Switzerland	ApyraMed is a live biotherapeutic as an enhancer of immune checkpoint blockade. Exploits the already marketed and safe Salmonella Ty21a vaccine strain (Vivotif®) .	Single Species	Solid Tumors Immuno-oncology; C. Difficile
OM Pharma	Switzerland	OM-85 - Bacterial Lysatea of 21 common bacterial respiratory pathogens,	Lysate	Recurrent wheezing episodes
PharmaBiome	Switzerland	Faecal Microbiome Transfer (FMT)	FMT	Intestinal Inflammation

Organisation	Location(s)	Lead Development Science	Class	Disease Indication
Redbiotec	Switzerland	Not cited	Not cited	Pancreatic Cancer
T3 Pharmaceuticals AG	Switzerland	T3P-Y058-739 - a genetically modified strain of the bacterium Yersinia enterocolitica	GMO	Solid Tumours Immuno-oncology
4D Pharma	UK	MRx0518 is a live biotherapeutic product consisting of a lyophilised formulation of a proprietary strain of bacterium, isolated from a healthy human faecal sample.	Single Species	Solid Tumours
EnteroBiotix	UK	Faecal Microbiota Transplantation (FMT)	FMT	Not cited
Microbiotica	UK	Live bacterial therapeutics (LBT) are defined consortia of precision-selected naturally occurring, safe bacteria, manufactured and dosed orally in a capsule.	Consortia	Ulcerative Colitis & Immuno-oncology
OptiBiotix Health	UK	Lactobacillus plantarum LPLDL	Single Species	High cholesterol
veMico	UK	Integrate sequencing & informatics technologies with synthetic biology to identify and advance promising molecules encoded in gut microbial DNA.	Not cited	Not cited
Actym Therapeutics	USA	ACTM-838 is Actym's lead clinical development candidate for the treatment of solid tumours. The therapeutic candidate is based on the company's immunotherapy platform called STACT (S. Typhimurium-Attenuated Cancer Therapy).	Single Species	Immuno-oncology

Organisation	Location(s)	Lead Development Science	Class	Disease Indication
Alveolus Bio	USA	AB1000 - novel inhaled live biotherapeutics that address airway dysbiosis and neutrophilic inflammation.	Single Species	Chronic Obstructive Pulmonary Disease (COPD)
Ancilia Biosciences	USA	Harness CRISPR's natural function to enable a new generation of LBPs with engineered immunity to viral Phages.	CRISPR enabled phage	Not cited
AOBiome Therapeutics	USA	AOBiome's B244 is a patented, proprietary, topical formulation incorporating a single strain of beneficial AOB, Nitrosomonas eutropha D23. B244 is designed to repopulate the skin microbiome with AOBs normally found on the body, but frequently stripped away by most soaps. Once deployed on the skin, B244 converts ammonia to nitrite, which is known to have antibacterial properties, and to nitric oxide, a signaling molecule known to regulate inflammation and vasodilation.	Single Species	Atopic dermatitis
Artizan	USA	ARZC-001 is a novel, oral, gut-restricted potent small molecule inhibitor that is designed to neutralize a specific secreted factor of microbial-driven dysregulation and inflammation in the intestine.	Small Molecule	Inflammatory bowel disease (IBD)
Artugen	USA	ART 24 - Strains of Bacillus velezensis	Single Species	C. difficile infection (CDI)

Organisation	Location(s)	Lead Development Science	Class	Disease Indication
Assembly Biosciences	USA	ABI M201 is comprised of a rationally designed consortium of commensal bacteria that were selected based on ability to modulate ulcerative colitis	Consortia	Ulcerative Colitis
Atterx Biotherapeutics	USA	C-1205 is a lyophilized (freeze-dried) powder containing a harmless bacterium and a gelling ingredient	Single Species	Urinary tract infection (UTI)
Axial Biotherapeutics	USA	AB 2004 is a small molecule targeting the gut-brain axis	Small Molecule	Autism- Associated Irritability
Azitra	USA	ATR 04 (previously AZT 04) is a live biotherapeutic comprising of a non-secreting Staphylococcus epidermidis. The Staphylococcus epidermidis has been genetically modified to be auxotrophic to D-alanine as the active ingredient.	Single Species	Cancer therapy-associated rash
BioMed Valley Discoveries	USA	CNV-NT is derived from C. novyi wild type by heat treating the bacterial phage that carries the alpha toxin	Phage	Solid Tumours
Biopix	USA	Development of specialized organisms with specific attributes to occupy specific biome niches	Consortia	Infectious Disease
Bloom Science	USA	Not cited	Not cited	Refractory/Drug Resistant Epilepsy
BrickBuilt Therapeutics	USA	Live Biotherapeutic Microorganism	Consortia	Periodontitis

Organisation	Location(s)	Lead Development Science	Class	Disease Indication
ClostraBio	USA	Short-chain fatty acids (SCFAs) derived from commensal bacteria, particularly butyrate. block copolymers to which butyrate is covalently attached as a side chain. These polymers, known as CLB-004, have demonstrated controlled, extended release of butyrate in the ileum, cecum and colon in vivo: exactly where commensal bacteria produce butyrate in healthy individuals.	Natural Product	Ulcerative colitis (UC)
DeepBiome Therapeutics, Inc.	USA	Not cited	Not cited	Not cited
DermBiont	USA	DBI 001 is a human derived strain of Janthinobacterium lividum	Single Species	Atopic dermatitis
Destiny Pharma	USA	NTCD-M3 is a naturally occurring non-toxigenic strain of C. difficile which lacks the genes that can express C. difficile toxins.	Single Species	C. difficile infection (CDI)
Evelo Biosciences	USA	EDP1815 is an investigational oral medicine being developed for the treatment of inflammatory diseases. It is a non-live pharmaceutical preparation of a strain of Prevotella histicola	Single Species	Psoriasis
Federation Bio	USA	Proprietary oxalate-degrading gut microbes along with a diverse community of prevalent commensal bacteria	Consortia	Enteric hyperoxaluria

Organisation	Location(s)	Lead Development Science	Class	Disease Indication
Finch Therapeutics	USA	CP101 is an investigational microbiome therapeutic designed to deliver a complete microbial community in a one-time oral administration	Consortia	C. difficile infection (CDI)
FloraSeq LLC	USA	FS-0809 microbiota capsules	Consortia	C. difficile infection (CDI)
Forte Biosciences, Inc	USA	B-401, consists of three therapeutic strains of a commensal gram-negative bacteria.	Consortia	Atopic dermatitis
Holobiome	USA	Not cited	Not cited	Mental Health
Intralytix	USA	EcoActive™ bacteriophage therapy targeting adhesive invasive E. coli (AIEC)	Phage	Crohn's Disease
ISOThrive Inc	USA	ISOT-101 is a nondigestible, nonabsorbable prebiotic carbohydrate produced by bacterial fermentation of sucrose and maltose	Natural Product	Gastroesophageal Reflux Disease
J&J	USA	JNJ-72537634 - Not cited	Not cited	C. difficile infection (CDI)
Kaleido Biosciences	USA	KB295 is a novel glycan. KB295 modulates microbiome composition and metabolic output, thereby driving immune activity both locally and systemically to restore gut immune homeostasis	Natural Product	Ulcerative Colitis
Kibow Pharmaceuticals LLc	USA	Renadyl™," a synbiotic dietary supplement	Natural Product	Chronic Kidney Disease
Kintai Therapeutics	USA	KTX-0200, an oral small molecule	Small Molecule	Obesity
Locus Biosciences	USA	LBP- ECO1 - CRISPR Cas3-enhanced bacteriophage	CRISPR enabled phage	Urinary tract infection (UTI)
LUCA Biologics	USA	Live Bacterial Therapeutics	Consortia	Urinary tract infection (UTI)

Organisation	Location(s)	Lead Development Science	Class	Disease Indication
MarvelBiome, Inc.	USA	Focused on isolating, identifying, and characterizing microbial populations for novel therapeutic applications	Consortia	Not cited
Nextbiotix	USA	Enhanced bacteriophages	Phage	Not cited
Notitia Biotechnologies	USA	NBT-NM108, a novel botanical-based fixed-combination drug, to modulate the gut microbiota	Natural Product	Suspected or Confirmed Symptomatic COVID-19
Novome Biotechnologies, Inc	USA	NOV-001 is a first-of-its-kind combination product made up of NB1000S, a proprietary microbial strain that Novome genetically engineered to degrade oxalate, and NB2000P, a seaweed-derived prebiotic polysaccharide, which acts as a privileged carbon source for NB1000S	GMO	Enteric hyperoxaluria
Osel	USA	LACTIN-V contains Lactobacillus crispatus CTV-05, a single strain of hydrogen peroxide-producing vaginal Lactobacillus	Single Species	Bacterial Vaginosis, Urinary tract infection (UTI) & IVF
Pareto Bio	USA	Consortium of live bacteria	Consortia	Food Allergies
Persephone Biosciences	USA	Not cited	Not cited	Covid, solid tumours
Rebiotix (Ferring)	USA	RBX2660 is an enema-based product derived from human stool.	Consortia	Crohn's Disease
Rise Therapeutics	USA	R-2487 is a probiotic encapsulated biologic that has the unique ability to induce specific populations of T regulatory cells.	Not cited	Autoimmune disease
SciBac Inc.	USA	SCB 203 is a single strain inhaled biotherapeutic containing live lactobacillus hybrid	Single Species	Cystic Fibrosis

Organisation	Location(s)	Lead Development Science	Class	Disease Indication
Scioto Biosciences	USA	SB-121 - Lactobacillus Reuteri With Sephadex® and Maltose	Single Species	Autistic Disorder (AD)
Second Genome	USA	SG-3-00802 a novel microbiome-derived peptide, SG-3-00802	Peptide	Immuno-oncology
Seres Therapeutics	USA	SER-109 is a first-in-class investigational microbiome therapeutic, administered orally The FDA has granted SER-109 Breakthrough Therapy Designation and Orphan Drug Designation.	Consortia	C. difficile infection (CDI)
SFA Therapeutics, Inc	USA	Small-molecule drugs derived from natural substances produced in the human microbiome	Natural Product	Psoriasis
Siolta Therapeutics	USA	Infant gut microbiome based live biotherapeutic product	Consortia	Atopic dermatitis, food allergy, allergic asthma
Solarea Bio	USA	Novel sources of microorganisms with probiotic potential	Consortia	Inflammatory Conditiion
Stellate Therapeutics	USA	STL-101 is a synthetic form of queuine, a metabolite made exclusively by bacteria	Small Molecules	Parkinson's disease
Symberix	USA	SBX-101 a bacterial β-glucuronidase inhibitor	Small Molecules	Intestinal toxicities from antineoplastic agents, and NSAID
Synlogic Inc	USA	SYNB 1934 is an engineered E. coli Nissle strain	GMO	Phenylketonuria (PKU
Tenza	USA	Tenza reprograms symbiotic bacteria to administer medicines directly to the organs they naturally inhabit. Uses a ML-powered, synthetic biology platform that enables us to engineer a wider diversity of bacteria to produce higher yields of drugs than ever before.	Consortia	Not cited

Organisation	Location(s)	Lead Development Science	Class	Disease Indication
VastBiome	USA	Mining the gut microbiome for small molecules to treat immunological disorders and advance immunotherapy. Using artificial intelligence and synthetic biology, VastBiome indexes the microbiome for molecules with therapeutic properties.	Small Molecules	Immuno-oncology
Vedanta Bioscience	USA	VE303 is an orally administered, rationally defined bacterial consortium	Consortia	C. difficile infection (CDI)

Appendix 2 – Microbiome Pharma Service Providers

Organisation	Location	Services
Luina Bio Pty Ltd	Australia	Experienced in producing live biotherapeutic products, with both aerobic and anaerobic organisms, includes the development of scalable and fully closed axenic production processes.
BJP Laboratories	Australia	Offers unlimited access to a large variety of probiotic strains, inclusive of clinically studied strains, branded and generic strains, BJP services offer solutions to the therapeutic, dairy, food and agriculture sectors.
Microbiome Insights	Canada/Ireland	Provides end-to-end microbiome sequencing and comprehensive bioinformatics analysis. MBI has supported over 670 microbiome studies from basic research to commercial R&D and clinical trials.
Vaiomer	France	Contract research organization with expertise in tissue and blood microbiota. focuses on the molecular interaction between the microbiome and host cells in cardiometabolic diseases. In addition, the company provides a set of methods for metagenomic sequencing in tissues as well as for the quantitation of bacterial rDNA and bacterial translocation markers in blood.
Biose Industrie	France	CDMO - Cites expertise in Microbiotic candidates - Aerobic & anaerobic, Consortia & multi or single-strains, Commensal, and delivery GMOs.
Biomeostasis	France	Pre-clinical Contract Research Organization (CRO) that offers in vivo and complementary research services in the metabolic & GI Diseases field. For over 9 years, Biomeostasis has assessed the efficacy and mechanisms of action of health products that aim at preventing and/or treating conditions such as Obesity, Diabetes, NAFLD/NASH or IBD.
Wacker Biotech	Germany	Services cover cell banking, process & analytical development and the GMP manufacturing for clinical & commercial supply.
Eurofins Genomics	Germany	Offers INVIEW Microbiome Profiling 3.0 (NGS) & INVIEW Metagenome

Organisation	Location	Services
BitBiome	Japan	Provides next-generation microbiome analysis using “single-cell genomics” technology
Bio-Me	Norway	Offers a wide range of proprietary solutions to facilitate academia and pharma researchers each step of the gut microbiome analysis process. Our main services include: Gut microbiome analysis – PMP™ technology Starting from purified DNA, Bio-Me’s Precision Microbiome Profiling (PMP™) is a novel targeted approach using quantitative PCR – an attractive alternative to traditional sequencing analysis. PMP™ offers encompass PMP™ Broad Panel, as well as custom-made assays and solutions.
Ardigen	Poland	Bioinformatics - AI evaluation of metagenomes
ChunLab	South Korea	Claims to be the world's leading specialist in next generation sequencing and bioinformatics in the fields of microbial genomics, metagenomics and transcriptomics. Has designed a one-stop fully integrated NGS sequencing to bioinformatics pipeline.
Microviable Therapeutics	Spain	Offers the analysis of the composition and functionality of the intestinal microbiota, from a stool sample, using next generation sequencing technologies (NGS) coupled with advance bioinformatics.
BiomeHub	Spain	Next Generation Sequencing (NGS) and bioinformatics solutions to achieve rapid identification and characterization of microorganisms
MetaboGen	Sweden	MetaboGen has built a platform that integrates top-of-the line metagenomic data analysis with strain identification and subsequent development as well as clinical programs, to ensure successful development of novel assets. The platform allows the study of the microbial composition and reveal key microbial community members in various conditions, and to study the microbiome-host interactions in order to develop means for microbiome modulation and targeting.
Inpac Probiotics	Sweden	Packaging of Probiotics
Cerbios-Pharma SA	Switzerland	CDMO offers: Strain selection and genetic study, cGMP media, Fermentation & stabilization studies Downstream processing. Analytical methods development and validation. Use of DoE and QbD in the various project stages

Organisation	Location	Services
BacThera	Switzerland/Denmark	CDMO offers a set of services across the live biotherapeutic product value chain, from technical development right through to cGMP manufacture and release of drug substance and drug product.
Lifebit Biotech, Ltd	UK	Offers a new bioinformatic gut microbiome analysis product
Quay Pharma/SGS	UK	Offers formulation development and licensed for the clinical manufacture of live biotherapeutics products for digestive, urogenital and pulmonary delivery.
Cobra Biologics	UK/USA	Offers scale up and manufacturing of customers' live biotherapeutic microbiota products, manufacturing to cGMP standards for pre-clinical, clinical and commercial scale.
CosmosID	USA	Offers Next-Generation Sequencing (NGS) and industry-leading bioinformatics solutions to achieve rapid identification and characterization of microorganisms for pharmaceutical R&D, molecular diagnostics, public health, food safety, agriculture, and environmental applications.
BiomeSense	USA	Developing novel technologies to enable the collection, storage, and analysis of daily human gut microbiome profiles.
DIVERSIGEN	USA	Provide microbiome sequencing and analysis that powers microbiome discoveries in small startups, Fortune 500 companies, the labs of academic researchers, and direct-to-consumer companies.
Ginko bioworks	USA	Ginkgo's cell programming platform for building and testing thousands of microbial strains to accelerate progression of early preclinical leads to drug candidates optimized for further clinical development.
Nexilico, Inc	USA	Early-stage computational biology startup with a mission to advance microbiome and precision medicine R&D by developing the next generation of predictive microbiome precision medicine technologies to improve drug design and development as well as clinical outcome for a range of therapeutics.

Organisation	Location	Services
The Biocollective LLC	USA	Has built the most comprehensive platform to develop innovative microbiome therapeutics: to Collect better samples, Connect high quality data, and Correct our most urgent health conditions. The BioCollector Kit™ is a patented system for simplified, collection of quality, standardized, whole stool samples. Used by customers like Harvard's Dana-Farber Cancer Insitute, The University of Chicago, and AXIAL Biotherapeutics. Our ick-free system captures high-quality samples of the whole stool. With BioCollector™ any research is instantly comparable and repeatable for multi-omic analysis — from genomics to metabolomics to isolation and culturing."
Arranta Bio	USA	CDMO offers integrated process development and manufacturing, Drug substance process development, Drug product formulation development. Analytical development, qualification, and validation, cGMP clinical and commercial manufacturing drug substance and drug product, QC release and stability testing, cGMP cell banking, Process characterization, CMC regulatory services, Custom process establishment, manufacturing and strategic partnerships.
List labs	USA	CDMO offers integrated process development and manufacturing, Drug substance process development, Drug product formulation development. Analytical development, qualification, and validation, cGMP clinical and commercial manufacturing drug substance and drug product, QC release and stability testing, cGMP cell banking, Process characterization, CMC regulatory services, Custom process establishment, manufacturing and strategic partnerships.
Universal Stabilization Technologies	USA	Offers stabilization & delivery enabling technology for your microbial and biological products

Appendix 3 - Scottish Pharma Services

Company	Location	Services
Aridhia	Glasgow	Collaborative digital research
Sartorius Stedim BioOutsource	Glasgow	BioOutsource offers comprehensive biologics testing, with early success in providing analysis and support for biosimilar development followed by expansion into the new biological entity (NBE) space. BioOutsource also provides comprehensive cell line characterization, cell bank manufacturing services, and a broad range of biosafety testing. Their expertise in assay development and optimization has enabled the creation of a range of platform methodologies facilitating the quick development of critical bioassays as well as off-the-shelf assays designed to support biosimilar comparability studies.
SGS Vitrology	Glasgow	Biosafety testing services for biologics
Bioreliance (Merck)	Stirling/Glasgow	Biosafety & Associated Services, Vaccine manufacturing, gene therapy products, and large-scale production
Charles River	Tranent	Early-stage contract research organization (CRO), offers a diverse portfolio of discovery and safety assessment services
Ingenza	Midlothian	Applies its proprietary synthetic biology to manufacture chemicals, biologics, pharmaceuticals and biofuels
Macfarlan Smith Limited	Edinburgh	Comprehensive contract manufacturing facility ranging from the development of novel synthetic processes, through lab-scale production to the provision of multi-tonne custom synthesis, including the toll extraction of active principles from natural products.
Quotient Clinical	Edinburgh	Quotient's proprietary and unique Translational Pharmaceutics platform integrates clinical testing with formulation development and real-time GMP manufacturing.
PPD Development	North Lanarkshire	Provides a comprehensive clinical development portfolio featuring Phase I-IV and consulting services.
Quintiles	West Lothian	Offers clinical and laboratory services in Edinburgh that include assay development services.
Biocair	West Lothian	Specialised global logistics company for the pharmaceutical, biotech and life science industries.

Company	Location	Services
4Front Medical Solutions	Glasgow	Clinical Trial Patient Recruitment
Carnegie Clinical Research Ltd	Fife	Clinical trial project management and monitoring services
Castle Pharmacovigilance Limited	Edinburgh	Pharmacovigilance consultancy services
Clinical Monitoring Services Scotland (Cms Scotland Ltd)	West Lothian	Provides a range of clinical monitoring services including SOP preparation and development; Protocol writing and CRF design; Ethics Committee submissions; Trial planning; Trial monitoring; Report writing; Auditing; Data validation/coding; and Project management.
Clinical Start Up Solutions	South Lanarkshire	Specialising in Study Start Up for clinical trials within the UK and Ireland. T
Clinpal	Stirling	Clinpal is the first end-to-end clinical research platform purpose-built for virtual, hybrid and direct-to-patient studies
Clintec	Glasgow	Provides functional service expertise in Study Start-up, Regulatory Affairs, Clinical Monitoring, Project Management, Patient Recruitment and Retention, Quality Assurance, Medical Writing, Data Management, Medical Monitoring and Global Clinical Management.
CROM Source	Stirling	Clinical trial management and staffing solutions for Pharmaceuticals and Medical devices covering Phases I-IV (Phase I in Verona)
Frontier Science (Scotland) Limited	Highlands	Non-profit organisation with expertise in clinical trials management
Icon Clinical	Edinburgh	Global provider of outsourced drug development services
Intelligent Clinical Limited	Glasgow	Provides a unique range of products and services to support clients from concept through to clinical trial
IQVIA	West Lothian	Clinical trial management
Karma Oncology Limited	South Lanarkshire	Specialized oncology clinical development company
Klinikos	West Dunbartonshire	Expertise in Resourcing for Field Based Activities of a Clinical Trial in Europe

Company	Location	Services
Medpace	Stirling	Clinical Trial management offering site monitoring, regulatory submission, site start up and project management. It is a full-service Clinical Research Organization (CRO) for the pharmaceutical and biotechnology industries and provides Phase I-IV core development services for drug, biologic, and medical device programs in multiple therapeutic specialities.
Onorach	Dundee	Clinical trials company that helps deliver clinical trials from phase I - IV
PHASTAR	North Lanarkshire	Provides statistical consulting and to summarise, analyse and report clinical trials.
Protrials Global Limited	Edinburgh	Offers project management, clinical monitoring and data management.
Quanticate Limited	Edinburgh	Offers statistical consultancy, statistical programming and analysis, data management, pharmacovigilance and medical writing solutions.
Synexus	Glasgow	Recruits' patients and runs clinical trials at its own dedicated research centres
Concept Life Sciences (a Malvern Panalytical brand)	Dundee	Cover all activities from target to clinic, including discovery chemistry, biology, DMPK, bioanalysis, toxicology and GMP manufacturing.
AskBio	Edinburgh	Inducible promoters
Cypex	Dundee	The patented technology underlying Cypex's products enables the expression of human drug metabolising enzymes in bacteria without the need for large modifications to be made to the proteins. It also offers contract services for custom protein expression.
Fixed Phage	Glasgow	The Fixed Phage technology irreversibly binds phage to almost any surface. This immobilisation allows phage delivery to targeted locations, extending the antibacterial activity of natural phage from days to years.
Merck Millipore	West Lothian	Provider of CRISPR gene editing technology
Aquila BioMedical (Malvern Panalytical)	Edinburgh	Pre-clinical CRO offering its clients academic models for lead compound testing in vitro and in vivo in Immunology, Inflammation and Neuroscience.

Company	Location	Services
Brainwave Discovery	Edinburgh	Established service business, providing custom humanised model and assay development services for any CNS disease, and drug testing services in our human neurodegenerative disease models for Alzheimer's, Parkinson's and Huntington's disease.
Carcinotech	Edinburgh	3D printed mini tumours using patient-derived cancer stem cells, primary cells, and established cell lines.
Censo Bio Ltd, an Axol Bioscence Company	Edinburgh	Genetically edited iPSC-derived models
Gut Research Unit (GRU)	Edinburgh	We are interested in understanding how the normal human gut works and the processes that lead to diseases such as Crohn's and Ulcerative colitis. Our vision and network We are a 'MELTING POT' of researchers - immunologists, chemists, biologists, clinical trialists, clinicians and data scientists - with a shared vision to translate science to medicine. We work closely with the Edinburgh IBD Science network, including clinical colleagues at the Western General Hospital and scientists at the Institute for Genetics and Cancer and Roslin Institute. We collaborate across Scotland with the Universities of Glasgow, Dundee, and Napier.
Reprocell	Glasgow	The company is experienced in human tissue research, stem cells and 3D bioengineered tissues, including sourcing, handling and experimenting on human functional tissues and the creation of 3D tissues and induced pluripotent stem cells.
Fios Genomics	Edinburgh	Microbiome Bioinformatics
Curia formerly Albany Molecular Research (Glasgow) Limited (Amri)	Glasgow	World-class sterile fill/finish and formulation development capabilities; development laboratories, liquid and lyophilized GMP manufacturing suites; and a dedicated cytotoxic manufacturing suite for liquid and lyophilized products.

Company	Location	Services
Almac Sciences (Scotland) Limited	Midlothian	Contract peptide manufacture
BDD Ltd	Glasgow	BDD's patent protected tablet: OralogiK™ is a timed-release technology; enabling consistent pH-independent delivery of drugs targeted to the colon. Exploiting the well documented transit times through the GI tract, OralogiK™ tablets can be designed to release the drug at a target time after dosing which will promote release in the colon.
DuPont Nutrition Manufacturing UK Limited	South Ayrshire	FMC Health and Nutrition offer product support and development resources starting with the industry's broadest and deepest range of hydrocolloid and cellulosic products
Encap Drug Delivery (NextPharma)	West Lothian	Liquid and semi solid filled capsule pharmaceutical products
Glycologic Limited	Glasgow	Active nutritional / pharmaceutical ingredients (ANIs / APIs) and delivery systems, all based on carbohydrates
BioClavis	Glasgow	We leverage the proprietary TempO-Seq® transcriptomic/genomic platform technology, capable of efficiently analysing large cohorts with customisable biomarker panels of tens to thousands of genes, quickly and inexpensively.
Ex Scienta	Dundee	In silico drug discovery
Biochem Qp Consulting Ltd	Glasgow	Contract QP Services Legal Batch Certification for your IMPs and Commercial products
Assured Micro Ltd	Glasgow	Isolates can be identified to genus or species level, depending on specific requirements, Grade of area under test and criticality in manufacturing process. Identification is important to assess the origin of contamination and to formulate corrective actions for contamination events. A minimum of Gram stain testing is recommended to establish possible source of contamination (e.g. Gram positive cocci are frequently Operator derived, whereas Gram negative rods may reveal an unknown water spillage/leak).
Assured Micro Ltd	Glasgow	MHRA GMP certified microbiology testing service company that offers a full range of Microbiology services. Our core business is environmental monitoring for Cleanroom environments and critical areas. Service industries include (but are not limited to) sterile manufacturing, biomedical, medical devices, pharmaceutical, and NHS.

Company	Location	Services
Blutest Laboratories	Glasgow	Microbiology contract research and development services to companies involved in the production of medical devices and antimicrobial products.
NCIMB	Aberdeen	Identify, compare, sequence, characterise and monitor microorganisms
DNA Sequencing Services (MRC)	Dundee	Provides a wide range of contract research products for DNA analysis and associated services.
Edinburgh Genomics	Edinburgh	Offers access to a wide range of genomics platforms including Illumina's NovaSeq technology, Pacific Biosciences Sequel IIe platform, and the Oxford Nanopore Technologies PromethION. This modular and flexible approach to providing the latest technologies, combined with expert knowledge across a broad range of applications, supports a large and diverse portfolio of scientific research projects. The EdGe team also offers a wide range of bioinformatics services, from data QC to genome assembly, variant identification, and interpretation, in addition to a programme of popular genomics and bioinformatics training workshops.
Eurofins Pharma Services	Edinburgh	Offers INVIEW Microbiome Profiling 3.0 (NGS) & INVIEW Metagenome (Ebersberg Germany)
Wobble Genomics	Edinburgh	Specializes in maximizing RNA and DNA sequencing efficiency
Q2 Solutions - Central Laboratories	Livingstone	clinical trial laboratory service
Cytomos	Edinburgh	Process Analytical for Biopharma production
Qpmed Global	Edinburgh	Assists and maintains regulatory compliance. Services include Auditing, Regulatory Inspections and Regulatory Affairs, Development of Quality Management Systems, Interim/Locum Quality Management and GxP Training.
Tepnel Pharma Services Limited	West Lothian	Provides regulatory compliant analytics in support of small and large molecule APIs, IMPs and finished products.
Arrayjet	Roslin	provide instruments and services to pharma, diagnostic and life science industries. Our products use inkjet technology for precision picolitre liquid handling. Arrayjet focus on printing biological samples to create tools for genomic and proteomic screening, patient stratification and clinical diagnosis.

Company	Location	Services
Tissue Solutions	Glasgow	Can also assist with the procurement of biofluids including cord blood, serum, plasma, urine, faeces, bone marrow, saliva, tears, sweat, sputum, synovial fluid, CSF, ascites, menstrual blood and breast milk. These can be provided from normal and diseased donors and collected to specific inclusion or exclusion criteria.
Bioascent Discovery Limited	North Lanarkshire	Storage and management service for externally owned compound collections
Catalent ltd	West Lothian	Catalent Ltd has cryogenic storage capabilities (liquid nitrogen at -186 C) with 900 pallets space of refrigerated storage capacity (2-8 C). The facility is licensed and MHRA approved for controlled drugs.