ONCE VSL#3®, NOW VISBIOME®

the Curious History of the De Simone Formulation Probiotic

Alteration of the gut microbiome for therapeutic benefit has become an important tool for physicians and patients in the dietary management of various gastrointestinal disorders. In recent years, the number of clinical trials evaluating various probiotic products has grown significantly. The following review will evaluate the history, and legal dispute, surrounding one of the worlds most clinically studied probiotics, the De Simone Formulation. Since its introduction in the early 2000s this product has been commercialized under several brand names, and more recently has been the subject of a massive international litigation concerning the ownership of the proprietary formulation and efforts to reverse engineer the product. This dispute exposed some of the shortcomings of the U.S. regulatory framework for microbial agents which, despite not being biologic drugs, are often used by physicians in therapeutic applications as medical foods. The story is important for physicians, patients, and the distribution agents of these product to consider as they recommend, commercialize, and ultimately consume these agents in the management of serious intestinal disorders.

The De Simone Formulation (VSL#3[i] produced before January 2016)

The De Simone Formulation probiotic - which was previously commercialized with the trademark "VSL#3" - has been the subject of extensive clinical investigation with over 70 human trials published in medical literature. In the mid 1990s, Professor Claudio De Simone, a researcher and clinician based out of Rome, Italy created several different prototype probiotic formulations. "Very Safe Lactobacilli" (VSL) was used to identify a technological platform characterized by combinations of strains at concentrations over 100 billion per gram. Given that all the prototypes contained a specific, extensive list of different genus, species and strain designations, the term "VSL" was used as an abbreviation[ii],

After initial trials showed positive results in the rare disease, pouchitis,[1] the product was licensed to VSL Pharmaceuticals, Inc. ("VSL Inc") by the inventor, Professor De Simone. VSL Inc began commercially manufacturing the product under Professor De Simone's license, and direction, in a business arrangement with Danisco USA, Inc., a large-scale probiotic manufacturer in Wisconsin (Danisco was ultimately purchased by Dupont®). Commercialization of the product in the U.S. market started in 2003 under the brand name "VSL#3," a registered trademark

i VSL#3 is a registered trademark of VSL Pharmaceuticals, Inc.

ii No generic nomenclature was available for the different mixtures under scrutiny and listing the individual strains -was simply too long to be practical for use as a "name"

chosen and owned by VSL Inc. After launch, the formulation was subject to numerous additional human clinical trials in the dietary management of irritable bowel syndrome, ulcerative colitis, pouchitis, hepatic encephalopathy, and other severe conditions. The formulation ultimately became one of the most widely recommended, and most clinically studied, physician managed probiotic products. Over 70 human clinical trials have been peer reviewed and published on the formulation as a medical food.

In 2014, Professor De Simone decided to terminate his relationship with VSL Inc as a result of a series of ongoing disagreements regarding the maintenance of certain production requirements of the product. Upon the expiration of agreements between De Simone and VSL Inc, De Simone exercised his rights to block VSL from accessing his formulation, which was made exclusively at the Dupont manufacturing facility. He also granted a new license to the startup company, ExeGi Pharma to commercialize the formulation. ExeGi Pharma committed to maintaining the production standards to De Simone's specifications. The trademarked name, "VSL#3", however, was never owned by De Simone and, therefore, the formulation could not be sold under the same name by ExeGi Pharma. In 2016, ExeGi launched the formulation under the name, "Visbiome."

After the natural expiration of the license agreement, VSL Inc was no longer able to access De Simone's formulation made at Dupont. As a result, VSL initiated a scheme to attempt to reverse engineer the formula into an imitation product which would replicate the original. This new "VSL#3" product became the focal point of the international litigation which played out in US Federal Court in Maryland.

New "VSL#3" vs Original VSL#3 (containing the De Simone Formulation) –

On the surface, the new formulation "VSL#3" maintained some similar characteristics to the original produced by De Simone. For example, both contain the same genus and species of bacteria and, on the label, the new "VSL#3" claims to contain at least 450 billion colony forming units (CFUs) per packet. However, while the two products maintain a veneer of similarity, there exists significant differences between the original VSL#3 (which contained the De Simone Formulation) and the new probiotic now sold under the name "VSL#3."

Of note, as of writing this analysis, new imitation "VSL#3" has not been the subject of any human clinical trials which have resulted in peer reviewed publications.

The original De Simone Formulation, previously sold under the name VSL#3, contains the following 8 individual strains which have been deposited at the *Deutsche Sammlung von Mikroorganismen und Zellkulturen* cell depository in Germany:

> *Lactobacillus acidophilus* DSM24735, *Lactobacillus plantarum* DSM24730, *Lactobacillus paracasei* DSM24733, *Lactobacillus delbrueckii* subsp. *bulgaricus* DSM24734, *Streptococcus thermophilus* DSM24731, *Bifidobacterium longum* DSM24736, *Bifidobacterium breve* DSM24732, *Bifidobacterium infantis* DSM24737

These cell lines are cultivated and blended in certain ratios to produce a specific biochemical and immunologic profile. During the legal battle it was discovered that new imitation "VSL#3", in fact, does not have the same strains in the same proportions.[16] The new Visbiome product conversely contains the exact De Simone Formulation, made by the original manufacturer Danisco (now Dupont), as was studied in IBS, ulcerative colits, pouchitis, hepatic encephalopathy, etc. The product name and packaging are the only changes between the original De Simone Formulation and Visbiome ("Visbiome" trade name vs "VSL#3").

Brief Summary of Available Comparative Clinical Data

Since the launch of the new "VSL#3" product (first in Europe, now in the US) several investigators in Europe have compared the two VSL#3 formulations and found striking differences between the two formulations. This data has now been peer reviewed and published in several medical journals including, *The Journal of Cellular Physiology, Frontiers in Pharmacology, PLOS One*, and *Endocrine, Metabolic, & Immune Disorders*.

A common theme of all the data sets available thus far, is that both the quantitative and performance characteristics of the new vs original "VSL#3" branded product are fundamentally different. It is important to note that these products contain living microorganisms as the active principle whose functional performance characteristics are different depending on a variety of factors, including how the strains were produced.[iii,iv] Extensive data supports that production and fermentation changes can result in changes to the performance characteristics of a bacterium.[2,3,4,5,6,7] Production characteristics cannot be quantitatively measured in the final product, therefore, one must compare the *performance characteristics* of the final product to determine if production changes impact the activity and overall effectiveness of the product. A proper comparison of the new vs original (U.S./Danisco) "VSL#3," is summarized below, including the quantitative and functional performance characteristics of the two products.

The following is a summary of several comparative studies performed by researchers in Europe comparing the original VSL#3 produced by Dupont (containing the De Simone Formulation) with the new imitation "VSL#3" made in Italy. In each case, the data has been peer-reviewed and published in independent medical journals. Twenty-eight individual academic medical researchers from multiple research centers and universities have participated in seven comparative clinical trials. The following is a summary of the key findings:

Biagioli et al. Metabolic Variability of a Multispecies Probiotic Preparation Impacts on the Anti-inflammatory Activity. Frontiers in Pharmacology. 2017[8]

Biagioli *et al,* represents the first *in-vivo* animal (mice) study comparing the original VSL#3 product (containing the De Simone Formulation) with the Italian made imitation VSL#3.

- Study used the classic dextran sulfate sodium (DDS) induced colitis in mice. This is a classic animal model of intestinal colitis and inflammation which has been applied in scientific analysis of medicinal compounds for decades.
- Colitis was induced in the mice who were then fed the De Simone Formulation, Italian imitation VSL#3, or no treatment.

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iii While probiotic supplements are not biologic drugs, the FDA's numerous guidance documents with respect to biologic drugs are important to consider. Specifically, the FDA notes that: "*In contrast to chemically synthesized small molecular weight drugs, which have a well-defined structure and can be thoroughly characterized, biological products are generally derived from living material- human*, animal, or microorganism- are complex in structure, and thus are usually not fully characterized."[iii] In the same guidance document, the FDA states: "*Because, in many cases, there is limited ability to identify the identity of the clinically active component(s) of a complex biological product, such products are often defined by their manufacturing processes. Changes in the manufacturing process, equipment or facilities could result in changes in the biological product itself and sometimes require additional clinical studies to demonstrate the product's safety, identity, purity and potency.*"

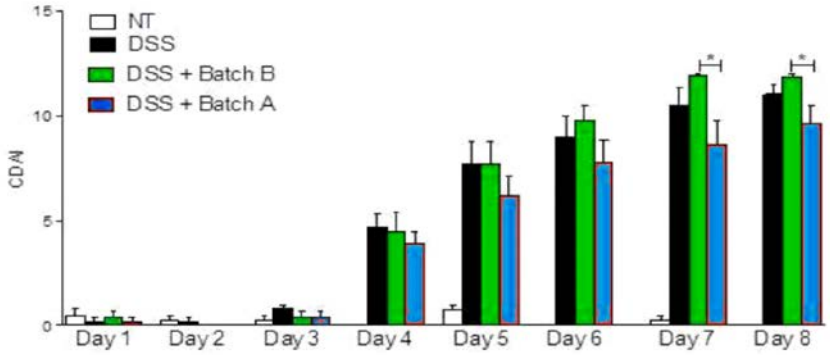
iv In 2016 the FDA Center for Food Safety and Applied Nutrition issued a Draft Guidance to Industry regarding *Dietary Supplements: New Dietary Ingredient Notifications and Related Issues (Page 66)* https://www.fda.gov/downloads/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/UCM515733.pdf
In this guidance the FDA takes the position with respect live microbial dietary ingredients which are candidate new dietary ingredients (NDIs): "FDA also considers the manufacturing process, including the fermentation, as an intrinsic part of the identity of an ingredient that is viable at the time of ingestion. We recommend that the fermentation and other parts of the manufacturing process relevant to safety and identity be described in detail in your notification, as recommended in questions VI.A.3 and VI.A.16." "FDA will pay particular attention to the viability of microorganisms in the NDI. The per-serving level of a viable microorganism depends on both the mass (in grams) and the viability (e.g., number of colony-forming units) of the organism in the final product. *The composition of the growth medium and the fermentation conditions of the organism are also relevant to the safety of the product, particularly when they alter the form of the organism* (e.g., spore vs. vegetative) or the composition of the ingredient (e.g., when the ingredient includes both the organism and the growth medium). "

- Mice treated with the De Simone Formulation (Batch A) experienced less in weight loss and a reduced intestinal inflammation. A reduction in intestinal permeability, and a reduction in severity of the colitis disease activity index (CDAI) were also observed, when compared to the non treated mice.
- Mice treated with new Italian imitation VSL#3 (Batch B) showed worsening CDAI index compared to the De Simone Formulation VSL#3 and no therapy. Shockingly, the animals treated with new imitation VSL#3 did worse than if they had no probiotic treatment at all.
- Italian imitation VSL#3 treated animals also had a worsening histopathology analysis and a 6-7 fold increase in intestinal permeability.

Table 1

Colitis Disease Activity Index in DDS induced Colitis Model

Batch B Italian imitation "VSL#3", Batch A VSL#3 containing De Simone Formulation



Cinque et al – VSL#3 probiotic differently influence IEC-6 intestinal epithelial cell status and function. Journal of Cellular Physiology. 2017[9]

- In this *in-vitro* study, multiple wound healing assays were used to evaluate performance characteristics of original VSL#3 containing the De Simone Formulation vs the new Italian made imitation using human non-transformed small-intestinal epithelial cell lines (IEC-6). Key findings (all performance metrics):
- Imitation VSL#3 caused clear morphological cell damage on IEC-6 cell lines with reduced cellularity.
- The De Simone Formulation product resulted in an enhanced rate of monolayer healing while imitation VSL#3 did not influence the closure rate
- The De Simone Formulation enhanced the formation of elongated and aligned stress fibers, while imitation VSL#3 had no effect.
- De Simone Formulation product was able to cause a total inhibition of H_2O_2-induced cytotoxic effects on the cell lines, whereas imitation VSL#3 was unable to produce such results.

Cinque et al. – Production Conditions Affect the In Vitro Anti-Tumoral Effects of a High Concentration, Multi-Strain Probiotic Preparation. Journal PLOS ONE. 2016[10]

- *In-vitro* study comparing qualitative and performance characteristics of the two formulations.

Performance Differences

- When evaluated for impact on cancer cell activity, De Simone Formulation was statistically significantly different from imitation VSL#3 in its capability to arrest proliferation of common cancer cell lines and in inducing apoptotic cell death in those cells.

Qualitative differences

- The percentage of live to dead bacteria ratios were found to be significantly different between the two products. High overall bacterial counts in the imitation VSL#3 and lower total viable (live) cell counts were observed, meaning that the Italian made product had a much higher quantity of dead bacteria (which is not an inert ingredient).
- The Italian imitation VSL#3 had approximately 130-150% more dead bacteria than the De Simone Formulation.

D'Ettorre et al. – p24 Levels in-vitro are affected positively or negatively depending by the production site of probiotic. Journal of International Society of Microbiota. Oct 2016[11]

- P24 is an antigen which makes up the core of the HIV virus. Blood concentrations of p24 go up in humans very shortly after HIV infection. Donor peripheral blood cells (PBMCs) were infected with the HIV-1 virus and incubated with the two different VSL#3 probiotics. The formulations had different effects on the HIV infected cultures. De Simone Formulation VSL#3 had an inhibitory activity as measured by p24 while new Italian imitation VSL#3 actually increased the levels of p24 (+8%).
- This data was presented at the famous Institut Pasteur in Paris and raises serious safety-related questions for the HIV community which need to be explored further. Again, it is clear that the performance characteristics of the two products are markedly different.

Trinchieri et al. - Efficacy and Safety of a Multistrain Probiotic Formulation Depends from Manufacturing. Frontiers in Immunology. Nov 2017[12]

- Eleven HIV-1 positive patients receiving antiretroviral therapy were treated for 6 months with the De Simone Formulation. The fecal metabolome was assessed using H-NMR spectroscopy with a focus on 1,3-dihydroxyacetone.
- In human subjects on De Simone Formulation 1,3-dihydroxyacetone decreased significantly.
- *In-vitro* the De Simone Formulation was able to metabolized 1,3-dihydroxyacetone while the bacteria in the Italian copy VSL#3 produced it confirming an additional functional difference between the two formulations.

Two other clinical comparisons, published in multiple peer-reviewed journals, have also found differences between the two formulations.[13,14]

A Federal Jury and U.S. District Judge Determine New VSL#3 and Original, Containing the De Simone Formulation, are Different Products

When De Simone left his partnership with the VSL Pharmaceuticals company he warned several times that making substantive changes to his formulation with different (less expensive) bacterial strains, or with altered production processes, could alter the performance of the product in ways that would be very difficult to predict without extensive testing *in vitro*, in animals and then in humans. Like most biologic medicinal agents, the nature of the De Simone Formulation product itself makes it inherently vulnerable to a paradigm in which changes to the manufacturing could impact the activity of the product even while it could have some similar features to the original (i.e. similar strain counts, genus and species). The only way to be sure that such the "new" product is in fact the same as the original is to perform in vitro studies, experiments in animals and then, if there are no "red flags", then move to human comparative "bridging" clinical trials to ensure consistent effects.[v]

After losing access to the De Simone Formulation, and faced with this technical reality, VSL Inc chose a reckless pathway: They created a whole new product, made the new formulation appear as similar as they could to the original, then launched it without any data in vitro, in animals and in humans. These actions created a paradigm in which users of the new "VSL#3" product became unwitting participants in a massive uncontrolled human experiment. The new formulation "VSL#3" was manufacturing in Italy and launched in mid 2016. De Simone, knowing the potential risk to patients, and to the legacy of his formulation, turned to the U.S. court system to prevent what he saw as a great injustice and a potential health risk. Unfortunately, the lax regulations in the U.S. for medical food products of this type left him no other remedial pathway. Thus, this new Italian imitation "VSL#3" became a core issue in a Federal Litigation that lasted over four years, only to be concluded recently.

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v It is for similar reasons that generic biologic drugs face a much more complex regulatory pathway with the FDA when compared to traditional, small molecule drugs. Biologic generic approvals almost always involve head-to-head comparative clinical outcome trials against the innovator product, a step normally not required for small molecule generic drugs.

During the Jury trial in 2018, De Simone and his partner ExeGi accused the sellers of VSL#3 in the U.S. (Alfasigma USA and Leadient Biosciences) of false advertising under the Lanham Act. De Simone and ExeGi contended that imitation VSL#3 was not the same as the original and thus advertising which claimed a continuity with the original formulation was false, and thus a violation of the false advertising laws. As noted by Judge Theodor Chuang in his Memorandum Opinion following the case, "*...at the heart of ExeGi's claim is that the falsity of Alfasigma's advertising is the representation that, in essence, its product is the exact same product, with the same formulation, as ExeGi's product,*"[15]

To prove their case, ExeGi and De Simon presented multiple scientific witnesses including three medical doctors and two PhD level scientists, which reviewed the extensive data supporting this key claim. A medical doctor and professor of gut physiology and pediatric gastroenterology at Harvard Medical School testified that, after reviewing the comparative data, "the new formulation from Italy is not ...comparable to the formulation that is from the United States." Likewise, an expert in the field of proteomics (the study of the entire set of proteins produced or modified by and organic system) stated that based on his proteomic analysis, "the two products were very different." The scientist concluded that there was approximately a 25 percent difference in protein expression between Italian imitation VSL#3 and the original formulation. He further determined that the difference in protein expression would likely result in a difference in performance, which could impact the medicinal value of the products.

A PhD level microbiologist and an expert on human gastrointestinal microflora, concluded that, based on his genetic analysis of the new formulation, the Italian VSL#3 actually only contained 7 strains of bacteria, not the 8 contained in the original formulation. Regulatory filings to Health Canada, filed by the Canadian distributor for VSL#3 in Canada, further supported the conclusion that the new Italian imitation VSL#3 only had 7 strains. He further testified that an analysis of the fermentation profiles of the two products showed that the they degrade compounds differently and thus function differently.

In addition to the previously stated evidence, the admissions of Chief Executive Officer of VSL Inc, Luca Guarna, added further support to the claims of ExeGi and De Simone. In testimony, he acknowledged that VSL Inc did not have access to the specific formulation, including the proportions of each strain, and thus arranged for scientists to reverse engineer the product. However, he admitted that "you can determine a certain range of the presence of the strains, but you cannot precisely assess the exact quantity of the strains." Their scientists were "not able to give a precise indication of the percentage of each strain contained in" in the original De Simone formulation. Rather. their scientists were only able to measure the amounts of each strain within a margin of 30 percent potential error.[15] With 8 individual strains, and a variability of 30% for each strain, this introduces an extreme level of variability supporting the conclusion that the new Italian VSL#3 did not contain the "original proprietary mix" or the "same proportions" of bacterial strains (marketing claims which lead in part to the false advertising verdict).

VSL Inc did present the opinion of one microbiologist in support of its argument that the two products were the same or similar, but this opinion was far outweighed by the overwhelming evidence presented by ExeGi and De Simone. No medical doctor supported the thesis of Alfasigma. After a three-week jury trial in Maryland, the jury found that Alfasigma USA and Leadient Biosciences were liable for false advertising under the Lanham Act and awarded $15 million in damages. Following the Jury verdict, in a response to post-trial motions from both sides, Judge Theodor Chuang of the U.S. District Court of Maryland[16] upheld the verdict finding in part that:

> "*...the evidence established that the VSL Parties senior management, specifically, Luca Guarna, the President and CEO of VSL, knew that in producing a new version of VSL#3 in Italy, they had not been able to precisely replicate the original proprietary mix, so the false advertising was deployed with the intent to confuse or deceive.*"[15]

The Court then went on to issue a permanent injunction aimed at "*curtailing such claims of continuity between Italian VSL#3 an the De Simone Formulation.*"

> "*The Court will thus permanently enjoin Alfasigma and Leadiant from making any claims in VSL#3 promotional materials that state or suggest a false continuity between Italian VSL#3 and the De Simone Formulation, including but not limited to statements claiming that VSL#3 continues to contain the "original propriety blend" or the "same mix in the same proportions.*
>
> *The VSL Parties will also be permanently enjoined from citing any clinical study performed on the De Simone Formulation or implying that any such study was conducted on Italian VSL#3."*

While the Judge did not find definitive evidence that that Italian VSL#3 is unsafe of clinically ineffective for all of its users, he did cite "public health" as a factor in considering the permanent injunction.

> "*...it is self evident that preventing false or misleading advertising is in the public interest in general," and that interest is particularly salient here because the false information 127- being circulated "pertains to issues of public health and ... well-being." PBM, 639 F. 3d at 28. As with the third factor, Alfasigma's contrary arguments generally focus on the scope and nature of the injunction that ExeGi seeks, rather than on the question whether any injunction is appropriate*."

The permanent injunction went into effect on June 20, 2019.

The De Simone Formulation Today

Following the original Jury verdict in 2018, and the more recent injunction, most of the major retail chains and pharmaceutical wholesalers in the United States have stopped the sale of VSL#3 products. Furthermore, six universities in the U.S. and Europe (including Stanford University, Emory, University of Wisconsin-Madison, and the University of Louisville) have all halted ongoing human trials on the copy product. Multiple journals have also started the process of amending historical publications to replace the brand name "VSL#3" with "De Simone Formulation."[17,18] The Cochran Review guideline for the treatment and prevention of pouchitis edited their guidelines recently to remove the term "VSL#3" from the publication and to replace it with the generic nomenclature "De Simone Formulation."[19] Additionally, The Clinical Guide to Probiotics, US and Canada editions, removed the term "VSL#3" from their guidelines and replaced the recommendation with the Visbiome brand name.

In Europe, the De Simone Formulation is commercialized by multiple entities under the name, Vivomixx and in the U.S. the brands are available under the names Visbiome and Visbiome Extra Strength. The product is also used in the veterinary field under the name Visbiome Vet, flowing several publications using the formulation in companion dogs with inflammatory bowel disease. The formulation continues to be produced under the direction of Professor De Simone by Danisco (now owned by Dupont®) in Madison, Wisconsin. Professor De Simone and his commercial partners are also working with multiple academic institutions conducting clinical research in a variety of new applications; including the dietary management of HIV related bacterial translocation, quality of life metric in autism spectrum disorder related neurological, and glycemic control in pre-diabetic adolescents.

The story highlights the need for more FDA regulation of the probiotic field as patients could be put at risk if not for the actions of the product inventor and the Federal court system in the United States. While medical foods contain generally recognized as safe (GRAS) ingredients there are legitimate safety issues to be concerned with as patients, confronted with a multitude of commercial options for probiotics, could unknowingly consume an untested product, thus forgoing the opportunity to benefit from a clinical proven option. In Canada, probiotics are regulated under stricter oversight and with an approval and management process analogous to a drug approval.[20] A similar process could be adopted in the U.S. for the benefit of patients and for the makers of legitimate, clinically evaluated products.

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