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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte SCOTT DORFNER[1]

Appeal 2019-001443
Application 13/162,129
Technology Center 1600

Before JEFFREY N. FREDMAN, JOHN G. NEW, and JAMIE T. WISZ, *Administrative Patent Judges.*

NEW, *Administrative Patent Judge*.

DECISION ON APPEAL

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[1] We use the word "Appellant" to refer to the "applicant" as defined in 37 C.F.R. § 1.142. Appellant identifies Tecoppa Biopharma, LLC as the real party-in-interest. App. Br. 4.

SUMMARY

Appellant files this appeal under 35 U.S.C. § 134(a) from the Examiner's Final Rejection of claims 93–118. Specifically, claims 93–116 stand rejected as unpatentable under 35 U.S.C. § 112, first paragraph, for lack of enablement.

Claims 93–118 stand rejected as unpatentable under 35 U.S.C. § 103(a) as being obvious over the combination of T. Arvola et al. *Prophylactic Lactobacillus GG Reduces Antibiotic-Associated Diarrhea in Children with Respiratory Infections: A Randomized Study*, 104(5) PEDIATRICS 1–4 (1999) ("Arvola"), D.L. Witsell et al., *Effect of Lactobacillus acidophilus on Antibiotic-Associated Gastrointestinal Morbidity: A Prospective Randomized Trial*, 24(4) J. OTOLARYNGOL. 230–233 (1995) ("Witsell"), Farmer (US 7,807,151 B2, October 5, 2010) ("Farmer"), and Fitzpatrick et al. (US 2009/0252708 A1, October 8, 2009) ("Fitzpatrick").

We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

NATURE OF THE CLAIMED INVENTION

Appellant's claimed invention is directed to a method of treating a patient with a formulation comprising: (1) a therapeutically effective amount of at least one antibiotic; and (2) a therapeutically effective amount of at least one probiotic material. Abstr.

REPRESENTATIVE CLAIM

Claim 93 is representative of the claims on appeal and recites:

> 93. A method of treatment of a patient having a non-gastrointestinal tract infection selected from bacterial sinusitis, a sexually transmitted disease of bacterial origin, pharyngitis, otitis, otitis media, bacterial bronchitis, bacterial pneumonia, a urinary tract infection, and skin and skin structure infections, cellulitis, abscesses, furuncles, impetigo, pyoderma, wound infections, acne, nail infections, chronic bacterial prostatitis, and pyelonephritis while simultaneously preventing a *Clostridium difficile* infection of a gastrointestinal tract of the patient comprising:
>
> administering a formulation to the gastrointestinal tract of the patient comprising at least one antibiotic in an amount sufficient to be systemically therapeutically effective for the nongastrointestinal tract infection of the patient and at least one probiotic material, wherein the formulation is a dosage form for delivery to the gastrointestinal tract and the antibiotic and the probiotic material are in physical contact with one another in the formulation whereby the nongastrointestinal tract infection is treated and the patient is prevented from developing a *Clostridium difficile* infection of the gastrointestinal tract.

App. Br. 23.

ISSUES AND ANALYSES

We agree with, and adopt, the Examiner's findings, reasoning, and conclusion that the claims on appeal are not enabled and are obvious over the combined cited prior art. We address the arguments raised by Appellant below.

A. Rejection of claims 93–116 under 35 U.S.C. § 112, first paragraph

Issue

Appellant argues that the Examiner erred in concluding that Appellant's Specification does not reasonably enable treating all claimed non-gastrointestinal disorders and/or infections. App. Br. 10; *see also* Final Act. 2.

Analysis

The Examiner finds that the scope of the claims encompasses prevention of *Clostridium difficile* infections for a long list of "non-gastrointestinal tract" diseases (claim 93), or for a long list of pathogens causing non-gastrointestinal tract infections that are also pathogens of gastrointestinal tract (claim 105), for several long lists of various and nearly all possible antibiotics (claims 95–99, 108–11) and for a large list comprising generic bacterial species (claims 101, 113). Final Act. 2–3.

The Examiner finds that guidance disclosed by Appellant's Specification is generic with regard to specific combinations of probiotic and antibiotic for specific patients under treatment. Final Act. 3. The Examiner similarly finds that the guidance in the two working examples disclosed by the Specification is limited to only two patients: (1) a patient diagnosed with pneumonia treated with levofloxacin compounded together with *Lactobacillus acidophilus* in a single capsule; and (2) a second patient with a middle ear infection treated with a suspension comprising amoxicillin, clavulonic acid and *L. acidophilus*. *Id.* The Examiner finds that the Specification discloses that the condition of patients was resolved without adverse gastrointestinal effects, but it is uncertain that the

Specification discloses whether or not patients were at any risk of developing of a *C. difficile* infection, because no bacteriological analysis for potential presence of *C. difficile* was performed or considered. *Id.*

The Examiner finds that the prior art teaches the unpredictability of probiotic administration, including treatments of seriously ill patients with sepsis, pneumonia, etc. Final Act. 3 (citing, e.g., L.E. Morrow, *Probiotics in the Intensive Care Unit*, 15(2) CURR. OPIN. CRIT. CARE 144–48 (2009) ("Morrow")). The Examiner finds that Morrow teaches that the success of a probiotic agent in any one clinical setting does not guarantee a similar in another. *Id.* (citing Morrow 147). Moreover, the Examiner finds that the claimed generic genus of probiotic bacteria, including *Lactobacillus* and *Bifidobacteria*, are sensitive to certain antibiotics including those that are listed in the pending claims. *Id.* (citing, e.g., S. Delgado et al., *Antibiotic Susceptibility of Lactobacillus and Bifidobacterium Species from the Human Gastrointestinal Tract*, 50(4) CURR. MICRIBIOL. 202–07, Abstr. (2005) ("Delgado")).

The Examiner concludes that it would have required undue experimentation to practice the invention as claimed, because of the limited amount of guidance and limited number of working examples in Appellant's Specification, the nature of the invention, the state of the prior art, the breadth of the claims and the unpredictable nature of the art at the time of invention. Final Act. 4. The Examiner further bases this conclusion due to the quantity of experimentation necessary to identify specific combination of antibiotics and probiotics for specific patients with specific diseases, the limited amount of guidance and limited number of working examples in the specification directed to treatment while preventing *C. difficile* infection, the

unpredictable nature of an invention directed to the use of generic bacterial species as probiotics in combination with any and all antibiotics, the unpredictability in the art with regard to probiotics and breadth of the present claims directed to unlimited lists of infections, antibiotics and generic bacterial species as probiotics. *Id.* (citing *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

Appellant argues that, contrary to the Examiner's findings, a review of the *Wands* factors illustrates that any experimentation required to perform the methods within the full scope of the invention is not undue. App. Br. 10.

First, Appellant argues that the level of required skill in the art is extremely high, requiring that a person of skill likely be a medical clinician with experience in diagnosis of infections and pharmacotherapy. App. Br. 11.

Next, Appellant argues that the claims are relatively narrow in scope; each of the treatable "non-gastrointestinal inflections" and the suitable "antibiotics" is recited in the claims and are fairly common conditions, the treatment of which would have been routinely encountered and/or studied by a person of ordinary skilled person in the art.[2] App. Br. 11. Similarly, Appellant contends, the claims recite the probiotic(s) that may be used to

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[2] Appellant actually states that the claims recite: "fairly common condition[s,] the treatment of which would have been routinely encountered and/or studied by the highly skilled person in the art…." We remind Appellant that the actual standard of enablement to be applied in an analysis under the first paragraph of 35 U.S.C. § 112 is that of a person of *ordinary* skill in the art. *See, e.g., In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970) (holding that "the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art") (footnote omitted)).

create the dosage form of the invention. *Id.* Appellant notes that the Specification provides guidance in the form of identification of the treatable Non-gastrointestinal infections, the suitable antibiotic(s) and/or the probiotic(s) that one may use to create the dosage form of the invention, as well as teaching related to the various known dosage forms that can be prepared for use in the methods. *Id.*

Appellant argues further that the nature of the claimed invention is an extension of a well-developed area of technology, *viz.*, medical treatment of infections using systemically administered antibiotics. App. Br. 11. Appellant asserts that the technology from which the invention extends cannot be characterized as nascent or frontier, rather, it is relatively predictable and any experimentation required to optimize success of the invention is quotidian to a medical practitioner, such as the person of skill in the art. *Id.* at 11–12. According to Appellant, the technology of the invention is no more unpredictable than the ordinarily and usual practice of pharmacotherapy, in which variations routinely occur because of the endless variety of patients' current physical and physiological makeups. *Id.* at 12. Appellant contends that the Examiner's reliance upon Morrow as establishing the unpredictability of the art is misplaced: Appellant argues that Morrow discloses, at most, the well-understood concept that prognoses of any type for critically ill patients in the Intensive Care Unit may be unreliable. *Id.*

We are not persuaded by Appellant's arguments.

> Section 112 requires that the patent specification enable "those skilled in the art to make and use the full scope of the claimed invention without 'undue experimentation'" in order to extract meaningful disclosure of the invention and, by this disclosure,

> advance the technical arts. Because such a disclosure simultaneously puts those skilled in the art on notice of the enforceable boundary of the commercial patent right, the law further makes the enabling disclosure operational as a limitation on claim validity. "The scope of [patent] claims must be less than or equal to the scope of the enablement. The scope of enablement, in turn, is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation."

Invitrogen Corp. v. Clontech Labs. Inc., 429 F.3d 1052, 1070–71 (Fed. Cir. 2005) (internal citations omitted).

In analyzing whether Appellant's Specification discloses sufficient guidance to permit a person of ordinary skill to practice the claimed invention without undue experimentation, we are guided by the factors set forth by our reviewing court in *Wands*. These factors include: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. *Wands*, 858 F.2d at 737.

With respect to *Wands* factor (2) and (3), Appellant's Specification addresses the dosages of both the antibiotic component and the probiotic component as follows:

> The unit dose and the dosage regimen of each the antibiotic(s) and the probiotic material(s) will be dictated by the specific antibiotic(s) and probiotic material(s) selected the dosage form and the medical particulars of the patient. In general, the unit dose and the dosage regimen will parallel that of the antibiotic if it were to be administered alone. For example, if the antibiotic recommended dosage is 200 mgs at two hour intervals, the antibiotic dosage in the formulation will remain substantially the

> same, as would the frequency of administration of the entire formulation. However, the therapeutically effective dosage of any specific antibiotic or agent will vary somewhat from antibiotic to antibiotic and/or probiotic material to probiotic material, patient to patient, and will depend upon the condition of the patient and the dosage form.

Spec. ¶ 26. More specifically, and with respect to the probiotic component, the Specification discloses that:

> In general, the probiotic material per unit dose may be preferred to be at about 2 billion colony forming units (CFUs) to about 50 billion CFUs, about 4 billion CFUs to about 10 billion CFUs, or about 6 billion CFUs to about 8 billion CFUs, depending on the medical particulars of the patient, including age and weight.

Id. ¶ 27.

Appellant's Specification provides two predictive examples, each a case study featuring a single patient. In Example I, "A 78 year old patient is diagnosed with nosocomial pneumonia and is prescribed a course of levofloxicin and probiotic material to be administered in single dose units …. each filled capsule contain[ing] a single dose of 750mg levofloxicin and the equivalent of 8 CFUs of probiotic material" daily for 14 days. Spec. ¶ 32. In Example II, the Specification discloses a study featuring "A 5 year old patient [ ] diagnosed with a middle ear infection" who is administered a 10 ml dose of "250 mg amoxicillin, 31.25 mg clavulonic acid in a potassium salt, and 4 CFUs of probiotic material" daily for 10 days. *Id.* at ¶¶ 34–36.

With the exception of these two examples, and the additional exemplary mention in paragraph [0026] quoted *supra*, Appellant's Specification does not disclose prescribed dosages for a given antibiotic for a given bacterial infection. We do not, however, find this determinative,

because the antibiotic dosage prescriptions for a given type of specific bacterial infection are well-known in the art of medicine and would be dependent upon the nature of the bacterial infection, the nature of the antibiotic, the age, health, size, and gender, etc., of the individual patient. The prescription of antibiotics for a given type of infection is routine and certainly well understood by practitioners of ordinary skill in the art of medicine (*Wands* factors 4–7).

The disclosures of the Specification with respect to the probiotic component of the claims, however, presents us with a conundrum. The Specification describes individual dosage units of "2 billion colony forming units (CFUs) to about 50 billion CFUs, about 4 billion CFUs to about 10 billion CFUs, or about 6 billion CFUs to about 8 billion CFUs, depending on the medical particulars of the patient, including age and weight." Spec. ¶ 27. However, the two individual case studies presented in Examples I and II consist of daily dosages of 8 and 4 CFUs[3] respectively, a very considerable disparity from the preferred dosages disclosed in paragraph [0027].

We find this large disparity between the preferred ranges recited in paragraph [0027] of the Specification, and those actually administered in the Specification's Examples I and II to be so wide (more than 9 orders of magnitude) so as to provide little reliable guidance to a practitioner of ordinary skill in the art, even as we acknowledge that a general dosage range for probiotics may well be generally known in the art. We conclude that, to practice the claimed invention successfully, a practitioner of ordinary skill,

[3] We note that if these dosages are in error, a fact not clearly in evidence of record, correction should avoid the inclusion of new matter.

confronted with a vast range of possible dosages – between 4 CFUs and 8 billion CFUs – would necessarily have to perform an undue amount of experimentation to find the proper dosage required to practice the invention. We consequently affirm the Examiner's rejection upon this ground.

B. Rejection of claims 93–118 under 35 U.S.C. § 103(a)

Issue 1: claims 93–104, 117, and 118

Appellant argues that the Examiner erred in finding that the combined cited prior art references teach or suggest a method using a single dosage form (containing both probiotic and antibiotic) to act systemically to treat a non-gastrointestinal infection and to prevent a *C. difficile* infection in the GI tract. App. Br. 16.

Analysis

The Examiner finds that Witsell and Arvola each teach methods of treatment with combined antibiotic-probiotic therapies of patients having nongastrointestinal infections and/or disorders while preventing gastrointestinal disorders, including antibiotic-associated diarrhea caused by infections, including by *C. difficile* infection. Final Act. 5.

Specifically, the Examiner finds that Witsell teaches that treatment of middle ear infections, in which concomitant administration of a probiotic bacteria *Lactobacillus* acidophilus together with two antibiotics, amoxicillin and clavulanate, is associated with a significant decrease in patient complaints of gastrointestinal effects during antibiotic therapy for otolaryngology patients. Final Act 5–6 (citing Witsell Abstr.). The Examiner finds that Witsell expressly teaches that patients were diagnosed

with otitis media, sinusitis and/or bacterial pharyngitis, and given antibiotic therapy for these conditions. *Id*. at 6 (citing Witsell 231). The Examiner also finds that Witsell additionally teaches that simultaneous administration of a probiotic with the antibiotic prevents and/or minimizes gastrointestinal infection by *C. difficile*. *Id.* The Examiner finds that Witsell teaches that the combined therapy resulted in a significant decrease in patient complaints of gastrointestinal effects during antibiotic therapy in patients with otolaryngological problems. *Id.*

The Examiner finds that Arvola teaches treatment of patients with pneumonia and middle ear infection by concomitant or simultaneous administration of a probiotic bacteria *Lactobacillus rhamnosus* with antibiotics, including penicillin, amoxicillin, cephalosporin, erythromycin, trimethoprim. Final Act. 6. The Examiner finds that administration of this therapy to patients with respiratory infections associated with otitis, pneumonia, bronchitis significantly reduced the incidence of antibiotic-induced disturbances of intestinal flora and diarrhea. *Id.* (citing Arvola, e.g., Table 1). The Examiner also finds that Arvola teaches that analysis of fecal samples in the treated patients for *C. difficil*e demonstrated that only 2 cases, (out of 199 patients), were found positive or *C. difficile*, indicating prevention of *C. difficile* infections. *Id.* at 6–7.

The Examiner finds that, although Witsell and Arvola teach concomitant and simultaneous administration of antibiotics and probiotics, neither reference teaches that "the antibiotic and probiotic material are in physical contact with one another in the formulation," as recited in claim 93. Final Act. 7. However, the Examiner finds, it was well known in the art at

the time of invention to provide both an antibiotic and a probiotic in the same one formulation. *Id.*

By way of example, the Examiner points to Fitzpatrick, which teaches co-administration of the probiotic bacteria *E. coli* and antibiotic(s) in one formulation, such as the same tablet or in a suspension. Final Act. 7 (citing Fitzpatrick ¶¶ 145, 153).

The Examiner also cites Farmer, which the Examiner finds teaches co-administration of the probiotic bacteria *Bacillus coagulans* and broad-spectrum antibiotic(s) in one formulation or in the same tablet/capsule. Final Act. 7 (citing Farmer col. 23, ll. 44–48). The Examiner finds that Farmer teaches that the probiotic in the formulation minimizes gastrointestinal infections including, *C. difficile*. *Id.* (citing Farmer col. 8, ll. 51–59).

The Examiner therefore concludes that it would have been obvious to a person of ordinary skill in the art to modify the co-administration methods of Witsell and Arvola by using a single formulation containing both antibiotic and probiotic components in contact with each other. Final Act. 7–8. The Examiner further concludes that a skilled artisan would have had a reasonable expectation of success in so modifying the methods of Witsell and Arvola, because both Farmer and Fitzpatrick teach the use of a single dose formulation of antibiotic and probiotic constituents. *Id.* at 8.

Appellant argues that Witsell and Arvola are each silent with respect to contemporaneous ingestion of the separate dosage forms of antibiotic and probiotic so that both forms are present in the gut at the same time, as is the consequence of the claimed method. App. Br. 16.

Appellant argues that neither Farmer nor Fitzpatrick cure the alleged deficiencies of Witsell or Arvola. App. Br. 16. According to Appellant, Farmer is directed to methods of treating infections at, and closely adjacent to the, the location where the therapy is applied. *Id.* at 16–17 (citing, e.g., Farmer col 8, ll. 41–63 (teaching that the Farmer method is directed to infections of the gastrointestinal tract); col. 11, ll. 55–57 (teaching treatment of vaginal infections by applying intra-vaginally); col. 11, ll. 61–65 (treating skin infections by applying topically to skin); col. 26, ll. 24–29 (treating oral infections by applying directly to the oral cavity).

Similarly, Appellant argues, Fitzpatrick teaches localized treatment in the GI track of anaerobe bacterial infection, such as microbial infection, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and pouchitis, which are caused by anaerobic bacteria. App. Br. 17.

We are not persuaded by Appellant's arguments. Arvola teaches that:

> Antibiotic use was continued for 7 to 10 days, and the dosage was divided into two or three doses and given every 8 to 12 hours. The patients were randomized by means of a computer program to receive placebo (microcrystalline cellulose) in capsule or 2 x 10^{10} colony-forming units of *Lactobacillus* GG in capsules given twice daily during the antimicrobial treatment.

Arvola 2. We agree with Appellant that Arvola does not expressly teach that the antibiotic and probiotic were administered simultaneously, nevertheless, the reference does teach that the constituents were administered on or about the same schedule over the course of the study. More importantly, there is no teaching or suggestion by Arvola indicating any reason why the antibiotic and probiotic could or should not be administered at the same time.

> Similarly, Witsell teaches that:
>
> [All patients] were counseled by the nursing staff to take the amoxicillin/clavulanate three times a day with food and eat a normal, balanced diet. Patients entered in the Augmentin-and-Lactinex group were also instructed to take the Lactinex (*L. acidophilus* and *L. bulgaricus*) as three tablets, four times daily (1.2×10^8 organisms/day).

Witsell 231. Again, although Witsell does not expressly teach simultaneous administration of antibiotics and probiotics, it teaches "concomitant administration" (Witsell 232) of the two on similar schedules and, again, there is no teaching or suggestion of Witsell that antibiotics and probiotics could not, for the sake of convenience, have been administered simultaneously.

> Farmer teaches:
>
> The present invention is discloses the recent discovery that non-pathogenic, lactic acid-producing bacterial species (i.e., "probiotic bacteria"), such as the exemplary *Bacillus coagulan*s, may be utilized in combination with antibiotic compounds or other functional anti-microbial drugs and supplements so as to form therapeutic compositions for use in ameliorating and/or controlling the colonization of pathogenic bacteria with the gastrointestinal tract of both humans and animals.

Farmer col. 10, ll. 51–59. Farmer also teaches that: "In a preferred embodiment, *Bacillus coagulans* spores, a therapeutically-effective concentration of an antibiotic, antifungal, etc., and, if so desired, various other components (e.g., bifidogenic oligosaccharide, binders, etc.) are encapsulated." *Id.* at col. 23, ll. 44–49. Finally, Farmer teaches that:

> In preferred embodiments of the present invention, the *Bacillus coagulans* strain is combined with a therapeutic dose of an antibiotic such as Gentamicin; Vancomycin; Oxacillin;

> Tetracyclines; Nitroflurantoin; Chloramphenicol; Clindamycin; Trimethoprim-Sulfamethoxasole; a member of the Cephlosporin antibiotic family (e.g., Cefaclor, Cefadroxil, Cefixime, Cefprozil, Ceftriaxone, Cefuroxime, Cephalexin, Loracarbef, and the like); a member of the Penicillin family of antibiotics (e.g., Ampicillin, Amoxicillin/Clavulanate, Bacampicillin, Cloxicillin, Penicillin VK, and the like); with a member of the Fluoroquinolone family of antibiotics (e.g., Ciprofloxacin, Grepafloxacin, Levofloxacin, Lomefloxacin, Norfloxacin, Ofloxacin, Sparfloxacin, Trovafloxacin, and the like); or a member of the Macrolide antibiotic family (e.g., Azithromycin, Erythromycin, and the like).

Id. at col. 23, ll. 18–33. We note that this list of antibiotics overlaps heavily with that recited both in Appellant's claims (see claims 95–99, 107–111) for treatment of non-gastrointestinal diseases, but also include the antibiotics used in Arvola and Witsell for treatment of non-gastrointestinal diseases.

Just as importantly, we find no teaching in Farmer expressly limiting the co-administration of probiotics and antibiotics at, or closely adjacent to the, the location where the therapy is applied, as Appellant argues. *See, e.g.*, Farmer claim 1, which recites:

> 1. A method for reducing gastrointestinal colonization by a pathogenic *Clostridium* bacterium, comprising identifying a mammalian subject having an infection with said pathogenic *Clostridium* bacterium, and orally administering a therapeutically-effective concentration of *Bacillus coagulans* bacteria within a pharmaceutically-acceptable carrier suitable for administration to the gastrointestinal tract of said subject, and further comprising the administration of a therapeutically-effective dose of an antibiotic, wherein the *Bacillus coagulans* bacteria reduce colonization of the pathogenic *Clostridium* bacteria.

Farmer teaches that the aim of its invention is to protect the bacterial infauna of the gastrointestinal tract from the deleterious effect, well-known in the art, of, *inter alia*, antibiotic therapy: "While the gastrointestinal microflora presents a microbial-based barrier to invading organisms, pathogens often become established when the integrity of the microbiota is impaired through stress, illness, *antibiotic treatment*, changes in diet, or physiological alterations within the G.I. tract." Farmer col. 2, ll. 49–53 (emphasis added).

Appellant points to the various exemplary embodiments where the antibiotics and probiotics may be administered locally, but such examples do not define the scope of the claims. *See Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (holding that "all disclosures of the prior art, including unpreferred embodiments, must be considered"). Rather, we understand the exemplary embodiments of Farmer as demonstrating the flexibility of simultaneous probiotic and antibiotic administration in different applications.

Similarly, Fitzgerald teaches that:

> The present invention is of a novel biotherapeutic composition containing a probiotic bacterial strain and an antibiotic to which the bacterial strain is resistant, which can be efficiently used in treating or preventing a condition caused by anaerobic bacteria. Specifically, the present invention is of a novel biotherapeutic composition, which comprises a probiotic Escherichia coli strain and an anaerobic bacteria antibiotic such as metronidazole, and of uses thereof in the treatment of gastrointestinal disorders such as pouchitis.

Fitzgerald ¶ 98. We acknowledge that Fitzgerald makes specific reference to diseases of the gastrointestinal tract, but Appellant points to no teaching

or suggestion of Fitzgerald that limits its invention to such applications. *See, e.g.*, Fitzgerald claim 1.

In the larger sense, however, Appellant's argument rather misses the point of the Examiner's rejection. Arvola and Witsell teach that probiotics and antibiotics can be co-administered on a daily basis for the treatment of non-gastrointestinal diseases while also protecting the gastrointestinal tract from *C. difficile* infections. The Examiner relies upon Farmer and Fitzgerald as showing that probiotics and antibiotics can be combined into a single dose without the constituents having adverse effects upon each other. "[I]t was manifestly obvious to combine two well-known drugs—which had previously been administered together—in a single tablet." *Ortho-McNeil Pharm., Inc. v. Teva Pharm. Industries, Ltd*., 344 Fed. Appx. 595, 602 (Fed. Cir. 2009). We agree with the Examiner's conclusion that it would have been obvious to combine the teachings of the references to arrive at Appellant's injection.

Issue 2: claims 105–116

Appellant argues that the Examiner erred because the combined cited prior art neither teaches nor suggests:

> [U]se of a single dosage form (containing both probiotic and antibiotic) to act to systemically treat a non-GI infection and to prevent a *Clostridium difficile* infection in the GI tract, where the non-GI infection is one caused by [any one or more of] *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, *Pseudomonas aeruginosa*, *Serratia marcescens*, Escherichia coli, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Streptococcus pneumonia parainfluenzae*, *Streptococcus pyogenes*, *Chlamydia*

> *pneumoniae*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Vibrio cholerae*, *Bacillus anthracis*, *Eikenella corrodens*, *Neisseria gonorrhoeae*, *Enterococcus faecalis*, *Enterobacter cloacae*, *Proteus mirabilis*, bacteria of the genus *Bacteroides*, including *Bacteroides fragilis*, bacteria of the genus *Fusobacterium*, and bacteria of the genus *Peptostreptococcus*, as recited in the claims 105–116.

App. Br. 17–18.

Analysis

Appellant argues that Witsell, Avola, and Farmer are silent on the pathogens infecting the patients in their studies. App. Br. 18. Appellant also notes that Fitzpatrick discloses bacterial pathogens, but only for the gastrointestinal infections its composition is intended to treat. *Id*.

The Examiner responds, by way of example, that Witsell teaches treatment of patients with sinusitis; and that sinusitis is commonly caused infections of bacterial origin including claimed *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Ans. 15.

We agree with the Examiner. Witsell teaches treatment of patients with bacterial infections including otitis media, pharyngitis, and sinusitis. Witsell 231. It is generally well known in the medical arts generally that certain bacteria are commonly associated with sinusitis, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. *See, e.g.*, Spec. ¶ 30. We are consequently no persuaded by Appellant's argument.

Issue 3

Appellant argues that the Examiner erred because a person of ordinary skill in the art would not have been motivated to combine the references to arrive at the invention recited in claims 93–118. App. Br. 18.

Analysis

Appellant argues that the methods of both Farmer and Fitzpatrick are intended for the treatment of a gastrointestinal tract infection or disorder that already exists, and that neither discloses a method that simultaneously treats a non-gastrointestinal tract infection or any non-gastrointestinal infection at all. App. Br. 18. Appellant also argues that neither Witsell nor Arvola teach a dosage containing the two claimed components, or that the antibiotic/antimicrobial should be taken contemporaneously with the probiotic. *Id.* Appellant argues further that neither reference teaches that contemporaneous co-administration is necessary or beneficial for any reason. *Id.*

Furthermore, Appellant contends, Arvola teaches away from use of probiotics to treat or prevent CD infection, because it explicitly discloses that the best method of treating such infection is still "use of [anti]microbials," which are locally administered into the gastrointestinal tract. App. Br. 18.

We are not persuaded by Appellant's arguments. As an initial matter, a reference can be said to teach away from an invention when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27

F.3d 551, 553 (Fed. Cir. 1994). However, teaching an alternative or equivalent method, however, does not teach away from the use of a claimed method. *In re Dunn*, 349 F.2d 433, 438 (C.C.P.A. 1965).

The passage of Arvola quoted by Appellant reads, in its entirety: "The most effective way to prevent antibiotic-associated diarrhea is still critical use of antimicrobials, as recommended recently for the treatment of acute otitis media in children. However, when antimicrobial treatment is indicated, *Lactobacillus GG* is a safe and useful adjunctive therapy to prevent diarrhea." Arvola 3–4. In other words, Arvola expressly recommends a combination of antimicrobial and probiotic in the treatment of diarrhea associated with the treatment of a non-gastrointestinal infection (otitis media) in children. We conclude that this does not constitute a "teaching away" by the Arvola reference.

With respect to the motivation to combine the references, Appellant contends that neither Witsell nor Arvola teaches or suggests that contemporaneous co-administration is necessary or beneficial for any reason. This is not the standard that we apply in determining obviousness; rather, it is what the combination of references would have taught or suggested to the person of ordinary skill in the art. *See, e.g.*, *In re Chevalier*, 500 Fed. App'x 932, 934 (Fed. Cir. 2013).

We agree with the Examiner that Witsell and Arvola both teach concomitant administration of antibiotics and probiotics in the treatment of non-gastrointestinal bacterial infections as a way of protecting against related gastrointestinal infection of *C. difficile*. Both Farmer and Fitzpatrick teach that antibiotics and probiotics can be combined into a single dosage form in which the constituents are in physical contact with each other. We

conclude, together with the Examiner, that a person of ordinary skill in the art would have been motivated, when considering treatment of non-gastrointestinal tract infections, to physically combine the antibiotic and probiotic to be administered into a single dosage form, to improve patient convenience and effective compliance with the regime and to prevent or minimize possible *C. difficile* infection.

Issue 4

Appellant argues that the Examiner erred because secondary considerations of nonobviousness are sufficient to overcome the Examiner's conclusion that the claims are *prima facie* obvious. App. Br. 18.

Analysis

Appellant first argues that the claimed invention satisfies a long-felt, though hitherto unrealized need. App. Br. 19. In support of this contention, Appellant points to the Declaration of Dr. Scott Dorfner, D.O. (the "Dorfner Declaration"), filed on March 30, 2017.[4] *Id.* According to Appellant, the inventive methods satisfy a long felt need for a way to prevent development of a *C. difficile* infection when undergoing systemic antibiotic treatment for a non-gastrointestinal infection that is clinically and practically effective. *Id.*

By "clinically effective," Appellant means that the prevention of a *C. difficile* infection occurs. App. Br. 19. By "practically effective," Appellant means that patients are able to comply with the binary dosage routine. *Id.* Appellant argues that "clinical medical practice" involves treating patients experiencing minor infections of various anatomical regions, excluding

[4] Dr. Dorfner is the inventor of record of the claimed invention on appeal.

infections of the gastrointestinal tract. *Id.* Appellant asserts that Dr. Dorfner states, by way of example, that an average general medical practice may see up to 15–20 patients per day with non-gastrointestinal tract infections, including, e.g., bronchitis, sinusitis, ear or eye infections, wound or skin infections, animal bite infections, pneumonia, nail infections, acnes, bacterial infections of a sexually transmitted origin, and urinary tract infections. *Id.* (citing Dorfner Decl. ¶ 13).

Appellant cites the Dorfner Declaration as providing an overview of how *C. difficile* infections constitute a common and harmful side effect of treating patients with non-gastrointestinal infections with antibiotics; Appellant contends that it is therefore apparent that the challenge of preventing *C. difficile* infection in patients undergoing a course of systemic antibiotic treatment for a non-gastrointestinal infection has been well appreciated for many years. *Id.* at 19–20 (citing Dorfner Decl. ¶¶ 15–20).

Appellant notes that the prior art, including Witsell and Arvola, teaches using administration of probiotics to prevent *C. difficile* infections have been made by providing probiotic supplements to patients undergoing antibiotic therapy. App. Br. 20. Appellant asserts that, in a clinical context, patients undergoing antibiotic treatment for infections are often unwilling or unable to take probiotic supplements, even when advised to do so by their prescribing doctor. *Id.* at 21.

Appellant points out that Arvola was published in 1999, and Witsell in 1995 and teaches other similar experiments dating back to the early 1990s. App. Br. 21. According to Appellant, in the ensuing 25-plus years since these experiments, no one has developed the claimed method which includes administration of the binary dosage form (i.e., a binary dosage form with

antibiotic and probiotic in contact with one another). *Id.* This, Appellant argues, is possibly due to the commonly held conception in the art that mixing an antibiotic with a probiotic would effectively react with or kill the probiotic, rendering it therapeutically useless. *Id.* Therefore, argues Appellant, no person of skill in the art considered a binary form as a potential solution to the two-fold problem of preventing *C. difficile* infection and increasing/improving patient compliance, prior to Appellant's invention. *Id.* (citing Dorfner Decl. ¶ 27).

We are not persuaded by Appellant's argument in this respect. Appellant's argument that there was a long-felt and hitherto unmet demand for their invention is entirely inferential and not supported by objective evidence of record; even Dr. Dorfner's opinion is not supported by any objective indicia of a long-felt need for the claimed invention.

> Where, as here, the obviousness determination turns on whether one of ordinary skill in the art would have expected that a particular formulation of an extended-release drug would be successful—in other words, would render a therapeutically effective treatment—*objective indicia* of failure of others and longfelt need are particularly telling.

In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig., 676 F.3d 1063, 1083 (Fed. Cir. 2012) (emphasis added). We accord due weight to Dr. Dorfner's explanation that secondary gastrointestinal *C. difficile* infections represent a medical problem, although we also note that Dr. Dorfner's statements to this effect are entirely unsupported by objective evidence of record. Nor does the Dorfner Declaration, or Appellant, provide *objective* evidence of a long-felt need, or evidence that others have unsuccessfully attempted to make or apply the solution Appellant claims for

its invention. In the absence of any such objective evidence of record, we do not find Appellant's arguments that its invention answers a long-felt need are persuasive.

Appellant next argues that, over the past five years, and in clinical experience with hundreds of patients, Dr. Dorfner has formulated and compounded multiple antibiotics for treatment of non-gastrointestinal infections with multiple species of probiotics into a single delivery system which patients have successfully used in the practice of the claimed method to avoid *C. difficile* infections. App. Br. 21 (citing Dorfner Decl. ¶ 29). Appellant argues that it was observed that gastrointestinal side effects, including antibiotic-associated diarrhea have been almost completely eradicated. *Id.* at 22. In addition, asserts Appellant, patient compliance and completion of therapy was also markedly improved, and the incidence of *C. difficile* infection and colitis, secondary to the administration of oral antibiotics, has also been significantly and vastly reduced in low, medium, and high-risk patients. *Id.*

We are not persuaded by Appellant's argument that the argued effects with respect to prevention and improved patient compliance constitute sufficient objective of surprising or unexpected results sufficient to overcome the Examiner's *prima facie* conclusion of obviousness. Again, we note that the Dorfner Declaration provides no objective evidence beyond Dr. Dorfner's unsupported assertions. *See* Dorfner Decl. ¶¶ 29–30. "It is well settled that unexpected results must be established by factual evidence. Mere argument or conclusory statements … [do] not suffice." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (citation omitted). Neither Appellant's Brief nor the Dorfner Declaration cite any such objective evidence of record. *See In*

re Am. Academy of Sci. Tech Center, 367 F.3d 1359, 1370 (Fed. Cir. 2004) ("[T]he Board is entitled to give such weight to declarations as it deems appropriate.")

Furthermore, "when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991). Appellant points to no such comparison of their allegedly unexpected or surprising results with any prior art of record. As such, we conclude that, in the absence of any objective evidence supporting the argument that Appellant's results are surprising or unexpected has little or no probative value, and we affirm the Examiner's rejection of the claims.

CONCLUSION

The Examiner's rejection of claims 93–116 under 35 U.S.C. § 112, first paragraph, is affirmed.

The Examiner's rejection of claims 93–118 under 35 U.S.C. § 103(a) is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
93–116	112, first paragraph	Enablement	93–116	
93–118	103(a)	Witsell, Arvola, Farmer, Fitzpatrick	93–118	
Overall Outcome			93–118	