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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte HEE-CHUL CHANG, BOK-KI KANG,
and JUN-KU KIM[1]

Appeal 2020-001371
Application 14/388,115
Technology Center 1600

Before ERIC B. GRIMES, JEFFREY N. FREDMAN, and JOHN G. NEW, *Administrative Patent Judges*.

NEW, *Administrative Patent Judge*.

DECISION ON APPEAL

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[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. The Appellant identifies the real party in interest as Daewoong Pharmaceutical Co., Ltd. Appeal Br. 3.

SUMMARY

Appellant files this appeal under 35 U.S.C. § 134(a) from the Examiner's Final Rejection of claims 33 and 36–42 as unpatentable under 35 U.S.C. § 103(a) as being obvious over the combination of Staab et al. (WO 2008/068217 A2, June 12, 2008) ("Staab"), Yada et al. (US 2010/0237530 A1, September 23, 2010) ("Yada '530"), Yada et al. (US 2011/0038898 A1, February 17, 2011) ("Yada '898"), and Obara (US 6,380,381 B1, April 30, 2002) ("Obara").[2]

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 pharmaceutical composition having a single dosage form comprising a compartment comprising olmesartan medoxomil; and a compartment comprising rosuvastatin or its salt, wherein said compartments are formulated in a separate form. Abstr.

REPRESENTATIVE CLAIM

Claim 33 is representative of the claims on appeal and recites:

33. A double-layer tablet comprising:

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[2] The Examiner also rejected claims 33–42 as unpatentable under 35 U.S.C. § 112, second paragraph, as indefinite. Final Act. 4. Claim 37 was also rejected under 35 U.S.C. § 112, fourth paragraph, as being of improper dependent form. Final Act. 8. These rejections were subsequently withdrawn by the Examiner. Adv. Act. 2 (filed February 15, 2019).

> a first layer comprising olmesartan medoxomil as a single active ingredient in an amount of 5 mg to 80 mg, and low-substituted hydroxypropyl cellulose (L-HPC) as a disintegrant in an amount of 19 wt.% to 21 wt.% based on the total weight of the first layer, wherein the L-HPC contains 5 wt.% to 16 wt.% of hydroxypropoxy[l] groups; and
>
> a second layer comprising uncoated rosuvastatin or a salt thereof as an active ingredient in an amount of 2 mg to 40 mg, and a disintegrant selected from the group consisting of crospovidone, L-HPC, croscarmellose sodium, carboxymethylcellulose calcium and a mixture thereof, in an amount of 2 wt.% to 20 wt.% based on the total weight of the second layer, wherein the L-HPC contains 5 wt.% to 16 wt.% of hydroxypropoxy[l] groups.

App. Br. 29.

ISSUES AND ANALYSES

We adopt the Examiner's findings, reasoning, and conclusion that the claims on appeal are *prima facie* obvious over the cited prior art. We address the arguments raised by Appellant below.

Issue 1

Appellant argues that the Examiner erred because the prior art fails to reveal any motivation for modifying the compositions taught by the prior art, or any reason that would lead to the specific combination. App. Br. 10.

Analysis

The Examiner finds that Staab teaches pharmaceutical compositions comprising a HMG-CoA reductase inhibitor, e.g., rosuvastatin, in combination with a renin angiotensin system inhibitor such as olmesartan. Final Act. 9 (citing Staab 3–4, 6–7). The Examiner finds that Staab teaches that these active ingredients can be located in different tablet layers that can be compressed as tablet layers or may be filled in capsules as granules. *Id.* (citing Staab Exs. 1–5). The Examiner finds that Staab teaches that the layered tablets can be made in the form of tablets comprising a core of HMG-CoA reductase inhibitor; or can be in form of bilayer tablet. *Id.* (citing Staab 10, 13, 15).

The Examiner also finds that Staab teaches that the tablet layer comprising the HMG-CoA reductase inhibitor may include 80 mg of that active agent, and that the tablet layer comprising the renin angiotensin system inhibitor may include 10–160 mg of the active compound. Final Act. 9 (citing Staab 11, 9). The Examiner finds that Staab teaches that the layers may include a disintegrant, such as hydroxypropyl cellulose and other cellulose derivatives, and/or crospovidone, in an amount of 1–20% of the total weight of the layer. *Id.* at 10 (citing Staab 8, 12–13).

The Examiner further finds that Staab teaches that compositions comprising the HMG-CoA reductase inhibitor (e.g., rosuvastatin) may also include such diluents as dibasic calcium phosphate, lactose monohydrate, and microcrystalline cellulose. Final Act. 10 (citing Staab 9–10).

The Examiner finds that Staab does not expressly teach compositions including olmesartan medoxomil, or the use of low-substituted hydroxypropyl cellulose. Final Act. 10. The Examiner finds, however, that

Yada '530 teaches formulations, including tablets, comprising olmesartan medoxomil that can be used in combination with other active ingredients, including rosuvastatin. *Id.* (citing Yada '530 ¶¶ 8, 41, 39). The Examiner finds that Yada '530 further teaches that such formulations may include low-substituted hydroxypropyl cellulose as a disintegrant that allows controlling and/or improving the dissolution properties. *Id.* (citing Yada '530 ¶ 30). The Examiner finds that Yada '530 provides an example of a formulation comprising olmesartan medoxomil, and low-substituted hydroxypropyl cellulose ("L-HPC") in an amount of 12.5 wt%. *Id.* (citing Yada '530 Example A-1, ¶ 54).

The Examiner also finds that Yada '898 teaches formulations comprising olmesartan medoxomil that provide controlled dissolution properties and allows minimizing interactions between the olmesartan and a second therapeutically active agent. Final Act. 10 (citing Yada '898 Title, Abstr., ¶¶ 14–15). To this point, the Examiner finds, Yada '898 expressly teaches the use of such disintegrants as L-HPC, croscarmellose sodium, crospovidone, and carboxymethylcellulose calcium. Final Act. 10–11 (citing Yada '898 ¶ 41). The Examiner finds that Yada '898 provides examples of formulations comprising olmesartan medoxomil and L-HPC) in an amount of about 20 wt%. *Id.* at 11 (citing Yada '898 Table 3).

Finally, the Examiner finds that Obara teaches L-HPCs having a hydroxypropoxyl content of 5–16 wt% can be used in oral solid pharmaceutical preparations for controlling the disintegration time of such preparations, providing good granulation characteristics and tablet properties. Final Act. 11 (citing Obara Abstr., col. 1, ll. 33–60, Table 1).

The Examiner finds that Obara explicitly teaches the use of L-HPC in an amount of 5-50% by weight. *Id.* (citing Obara col. 4, ll. 1–5).

The Examiner therefore concludes that it would have been obvious to a person of ordinary skill in the art was made to use an inhibitor of the renin-angiotensin system as olmesartan medoxomil and L-HPC as a disintegrant, as taught by Yada '530, Yada '898, and Obara, in the layered tablets taught by Staab. Final Act. 11. The Examiner reasons that a skilled artisan would have been motivated to combine the teachings of the references, because the artisan would have expected beneficial results, because the cited prior art teaches that compositions including olmesartan medoxomil provide controlled dissolution properties and allow minimizing interactions between olmesartan medoxomil and a second therapeutically active agent, i.e., rosuvastatin. *Id.*

Appellant argues that Staab teaches a pharmaceutical composition having a cholesterol-lowering agent in combination with an inhibitor of the renin angiotensin system (RAS). App. Br. 11 (citing, e.g., Staab Abstr.). Appellant asserts that these teachings of Staab constitute an extremely broad disclosure, and cover a virtually unlimited number of drug combinations, not to mention many possible types of formulations, excipients, combinations thereof, and relative amounts. *Id.* Appellant points to certain embodiments of Staab, in which the cholesterol-lowering agent may be a HMG-CoA reductase inhibitor, such as a statin, for example, as specified in independent claim 33. *Id.* However, Appellant asserts that Staab teaches that "[t]he terms HMG-CoA reductase inhibitor and statin are referred to in the description and the claims in a broad sense to include not only HMG-CoA reductase inhibitors or statins *per se* but also their salts, solvates, derivatives,

prodrugs, enantiomers, racemic mixtures, or polymorphs." *Id.* (quoting Staab 4; *see also id.* ("Additionally various available salts, solvates, derivatives, prodrugs, enantiomers, racemic mixtures, or polymorphs of the various HMG-CoA reductase inhibitors mentioned above may be used")).

Furthermore, argues Appellant, Staab defines an inhibitor of the renin angiotensin system ("RAS") extremely broadly. App. Br. 11. In support of this contention, Appellant points to Staab's teaching that:

> An "inhibitor of the renin-angiotensin system (RAS)" means any compound which in itself or upon administration blocks the negative effects of angiotensin II on the vasculature either by reducing the synthesis of angiotensin II or blocking its effect at the receptor. It includes pharmaceutically acceptable derivatives or salts of said compounds. Inhibitors of the renin-angiotensin system (RAS) known from the prior art include angiotensin converting enzyme (ACE) inhibitors, angiotensin II antagonists, also known as angiotensin receptor blockers (ARBs), renin inhibitors, and vasopeptidase inhibitors (VPIs).

Id. at 11–12 (quoting Staab 7).

Appellant therefore contends that Staab teaches an extremely large number of possible combinations, and provides no support for the Examiner's position that a skilled artisan would have made the specific combination of olmesartan and rosuvastatin recited in the claims. App. Br. 12. By way of example, Staab teaches that the "preferred HMG-CoA reductase inhibitor is simvastatin," and the Examples of Staab relate to agents such as simvastatin, telmisartan, or ramipril, but there is no teaching to select either olmesartan medoxomil or rosuvastatin. *Id.*

Appellant also asserts that nothing in the other references cures this alleged deficiency. *Id.* Specifically, Appellant contends that although Yada '530 and Yada '898 references may employ L-HPC in certain olmesartan

medoxomil formulations, neither reference teaches or suggests the combination with rosuvastatin at all, much less in a specific double-layer tablet or with the specific amounts of L-HPC claimed. *Id.* at 14. Appellant argues that Yada '530 teaches that increased dissolution is due to the effects of compression applied to the formulation. *Id.* (citing Yada '530, e.g., ¶¶ 9, 10–15). Therefore, Appellant argues, a person of ordinary skill would not have been directed to the use of L-HPC, much less the specific amount recited in currently pending claim 33. *Id.* at 14-15.

Appellant points to the First Declaration of Hee-Chul Chang, filed July 5, 2016 (the "First Chang Declaration"), one of the inventors of the application on appeal. App. Br. 15. Appellant contends that, according to Dr. Chang, the rate of dissolution of the prior art formulation, when formulated as part of a bilayer tablet, was much lower than when compared to a tablet according to Example A-1 of Yada '530, which contained only one active agent. *Id.* Therefore, Appellant argues, simply combining the L-HPC from the formulations of Yada '530 with Staab would not have led to a successful formulation. *Id.*

Similarly, Appellant argues, Yada '898 teaches that a calcium-containing additive should be used for addressing the drug interaction of olmesartan medoxomil with amlodipine contained in the same compartment with hydrochlorothiazide. App. Br. 15. Appellant asserts that a person of ordinary skill would not have had any reason to believe that the drug interactions relating to an entirely different combination of drugs (having different chemical structures and properties) would be applicable to the claimed combination. *Id.* Furthermore, argues Appellant, at best Yada '898 would have directed a skilled artisan to use a calcium-containing additive.

Id. Appellant contends that, although L-HPC is used in some of the examples, Yada '898 does not direct a person of ordinary skill to select L-HPC for the formulations of Staab, much less in the specific amounts recited in claim 33. *Id.* Indeed, argues Appellant, Yada '898 suggests Formula 7 (which uses 20% of L-HPC) has an unfavorable dissolution rate of olmesartan medoxomil, and describes formulations having carmellose calcium as disintegrant as providing favorable dissolution of olmesartan medoxomil. *Id.* at 15–16. Appellant argues that Yada '898 thus teaches away from using L-HPC and instead would have directed the skilled artisan to use carmellose calcium as the disintegrant. *Id.* at 16.

Appellant also argues that no reason is given by the Examiner with respect to why a person of ordinary skill would have selected the specific double-layer tablet having a first layer comprising olmesartan medoxomil and a second layer comprising uncoated rosuvastatin, much less the including the disintegrants that are recited in the claims, or the specific amounts claimed. App. Br. 12.

Appellant argues further that drug development is a highly unpredictable field, and it is not possible to predict, with any certainty, which combinations or formulations will be successful. App. Br. 12. Appellant asserts that there is nothing in the references that would have directed a skilled artisan to specific combinations of drugs, much less specific excipients or the relative amounts. *Id.* Furthermore, argues Appellant, even if a skilled artisan had attempted to combine the references, the prior art does not teach that there would have been a drug interaction when the two active ingredients are formulated in combination in a same layer or different layers, much less how to address such drug interaction. *Id.*

Appellant argues that it would not have been "obvious to try" to combine the teachings of the cited references to arrive at the claimed invention. App. Br. 13 (citing Final Act. 15). Appellant argues that this is because such an attempt at combination would have amounted to an impermissible effort to "vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *Id.* (quoting *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009)).

We are not persuaded by Appellant's arguments. Staab is directed to "a pharmaceutical composition comprising a coated HMG-CoA reductase inhibitor…, an inhibitor of the renin angiotensin system, and optionally further pharmaceutically acceptable excipients." Staab 3. Staab also teaches that "the present invention provides processes for the preparation of a pharmaceutical composition wherein the inhibitor of the renin angiotensin system and the HMG-CoA reductase inhibitor are comprised in different tablet layers…." *Id.* at 13.

More specifically, Staab teaches: "According to the present invention the various statins (HMG-CoA reductase inhibitors) that can be used comprise lovastatin, simvastatin, pravastatin, mevastatin, fluvastatin, cerivastatin, pitavastatin, *rosuvastatin* and atorvastatin. The preferred HMG-CoA reductase inhibitor is simvastatin" (emphasis added) and further notes that "various available salts, solvates, derivatives, prodrugs, enantiomers, racemic mixtures, or polymorphs of the various HMG-CoA reductase inhibitors mentioned above may be used." *Id.* at 4. Staab thus expressly includes rosuvastatin as one of the relatively limited number of

named HMG-CoA reductase inhibitors that can be used in its invention. Although Staab teaches that simvastatin is the preferred HMG-CoA reductase inhibitor, rosuvastatin is named as a useable constituent, and "all disclosures of the prior art, including unpreferred embodiments, must be considered." *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (quoting *In re Lamberti*, 545 F.2d 747, 750 (C.C.P.A. 1976)).

Furthermore, Staab teaches that:

> In a preferred embodiment of the present invention there is provided a dosage unit or tablet layer preferably comprising from 5 mg to 80 mg of simvastatin *or any suitable HMG-CoA reductase inhibitor* and preferably a dosage amount selected from 10 mg, 20 mg and 40 mg of simvastatin. Further the total weight of the single dosage unit of statin is identical for all strengths such as 150-250 mg.

Staab 11 (emphasis added). Staab thus teaches the use of a concentration of 5–80 mg of a suitable HMG-CoA inhibitor (including rosuvastatin), which largely overlaps the range of "2mg to 40 mg" of "rosuvastatin or a salt thereof" recited in claim 33.

Staab also teaches the use of:

> An "inhibitor of the renin-angiotensin system (RAS)" means any compound which in itself or upon administration blocks the negative effects of angiotensin II on the vasculature either by reducing the synthesis of angiotensin II or blocking its effect at the receptor. *It includes pharmaceutically acceptable derivatives or salts of said compounds*…. Examples of angiotensin II antagonists which can be used in a fixed dose combination with statins are candesartan, candesartan cilexetil, eprosartan, irbesartan, losartan, *olmesartan*, telmisartan and valsartan.

Staab 7 (emphasis added). Staab also teaches the use of olmesartan as an inhibitor of the renin-angiotensin system. Although Staab does not expressly teach "olmesartan medoxomil" as an active agent, as recited in claim 33, "olmesartan" and "olmesartan medoxomil" are used interchangeably by those of skill in the art, and refer to the same drug, with "olmesartan" being the brand name, as manufactured by Daiichi Sankyo, Inc. *See* The Marshall Protocol Knowledge Base, *Olmesartan (Benicar)*, *available at*: https://mpkb.org/home/mp/olmesartan (last visited September 25, 2020).

With respect to the concentration of RAS inhibitor employed, Staab teaches using "10–160 mg, and preferably 20–80 mg or 40–80 mg telmisartan, a comparable RAS inhibitor." Furthermore, Yada '530 teaches that "[a]lthough its [i.e., olmesartan medoxomil's] dosage amount varies depending on the symptoms, age and the like, an adult human is generally administered orally with 5 to 40 mg, once a day. Preferably, a tablet containing 5 mg, 10 mg, 20 mg or 40 mg is administered orally once a day." Yada '530 ¶ 51. Similarly, Yada '898 teaches that "[o]lmesartan medoxomil is marketed as OLMETEC (registered trademark) tablets or Benicar(R), and these contain 5 mg, 10 mg, 20 mg, or 40 mg of olmesartan medoxomil as active ingredient." Yada 898 ¶ 5. All of these teachings are encompassed by "olmesartan medoxomil … in an amount of 5 mg to 80 mg," as recited in claim 33.

With respect to the disintegrants in the HMG-CoA reductase inhibitor layer, claim 33 recites: "a disintegrant selected from the group consisting of crospovidone, L-HPC, croscarmellose sodium, carboxymethylcellulose calcium and a mixture thereof, in an amount of 2 wt.% to 20 wt.% based on

the total weight of the second layer, wherein the L-HPC contains 5 wt.% to 16 wt.% of hydroxypropoxy[l] groups." Staab teaches that the HMG-CoA reductase inhibitor layer is made by:

(a1) coating an HMG-CoA reductase inhibitor with a solution of polymer and subsequently adding antioxidant and suitable excipients to form a premix; or

(a2) coating an HMG-CoA reductase inhibitor with a solution of polymer and antioxidant and subsequently adding suitable excipients to form a premix; or

(a3) coating a mixture of HMG-CoA reductase inhibitor and antioxidant with a solution of polymer and subsequently adding suitable excipients to form a premix.

Staab 13–14. Staab teaches that suitable excipients of the HMC-CoA reductase inhibitor layer may include: "a diluent, binder, disintegrant, lubricant/glidant, chelating agent and coloring agent." Staab 12. Specifically, Staab teaches that:

> Suitable disintegrants may include one or more of but not limited to hydroxypropyl cellulose, carboxymethylcellulose, *calcium carboxymethylcellulose*, sodium carboxymethylcellulose, *croscarmellose sodium*, starch crystalline cellulose, sodium starch glycolate, hydroxypropyl starch, partly pregelatinized starch, *crospovidone* and equivalents thereof. Suitably the disintegrants may be present in a quantity ranging from 1 to 20% w/w relative to the total weight of the statin layer, preferably 5 to 20% w/w. The preferred disintegrant is Croscarmellose sodium.

Staab 13 (emphases added for species corresponding to those recited in claim 33); *see also id.* Examples 2, 3. Claim 33 also recites weight percentages of disintegrant in an amount of 2 wt.% to 20 wt.%, which is within the 1–20% by weight concentrations taught by Staab.

With respect to the RAS inhibitor layer, claim 33 requires: "low-substituted hydroxypropyl cellulose (L-HPC) as a disintegrant in an amount of 19 wt.% to 21 wt.% based on the total weight of the first layer." Staab teaches that, in addition to the active agent, "other excipients and adjuvants from binders, carriers, fillers, lubricants, flow control agents, crystallization retarders, solubilizers, coloring agents, pH control agents, surfactants and emulsifiers" may be included. Staab 8 (*see also* claim 19). However, Staab is otherwise silent as to what may constitute these excipients.

Yada '530 is directed to "an olmesartan medoxomil-containing drug product having an improved dissolution property." Yada '530 ¶ 8. Yada '530 also teaches that "in the present invention, other active ingredients may be included if necessary. As for such active ingredients, there can be mentioned for example,… HMG-CoA reductase inhibitors such as Pravastatin, Simvastatin, Atorvastatin, *Rosuvastatin*, Cerivastatin, Pitavastatin and Fluvastatin." *Id.* ¶ 39.

Specifically, Yada '530 teaches that, in its compositions: "As for the 'disintegrants' used, cellulose derivatives such as *low-substituted hydroxypropyl cellulose* [i.e., L-HPC], carboxymethyl cellulose, calcium carboxymethyl cellulose or internally crosslinked sodium carboxymethyl cellulose; crosslinked polyvinylpyrrolidone; or chemically modified starches/celluloses such as carboxymethyl starch or sodium carboxymethyl starch can be mentioned." Yada '530 ¶ 30 (emphasis added). Furthermore, Example A-1 of Yada '530 demonstrates, in Table A, a 20 mg dosage of olmesartan medoxomil combined with, *inter alia*, 20 mg of L-HPC as a disintegrant. *Id.* ¶ 54. The total mass of the formulation of Table A is 160

mg, which yields a concentration of L-HPC of 12.5 wt%, which is somewhat less than the range recited in claim 33.

Yada also teaches combination drugs with olmesartan medoxomil and amlodipine as active agents. Yada '898 Abstr. Yada '898 also teaches that, in its compositions "[e]xamples of 'disintegrants' that may be used include cellulose derivatives such as *low-substituted hydroxypropyl cellulose* [i.e., L-HPC], carboxymethyl cellulose, carboxymethyl cellulose calcium, or croscarmellose sodium; crospovidone; or chemically modified starches or celluloses such as carboxymethyl starch or carboxymethyl starch sodium." *Id.* ¶ 41 (emphasis added). Formulation 7 of Yada '898's Table 3 demonstrates a composition of olmesartan medoxomil (40 mg) and amlodipine with L-HPC at 20 wt% (84 mg out of 420 mg).

In summary, both Yada '530 and Yada '898 teach that L-HPC is a suitable disintegrant for combination therapies including olmesartan medoxomil and (in the case of Yada '530) rosuvastatin, an HMG-CoA reductase inhibitor, as claimed. The wt% values for L-HPC in the exemplary formulation of Yada '898 (20 wt%) is within the concentration range of "19 wt.% to 21 wt.%" recited in claim 33. Moreover, because the relative concentration of a disintegrant is a result-effective variable, determining the rate of disintegration of the composition, we find that a skilled artisan would be able to optimize the concentration of L-HPC within the ranges recited by the combined references and claim 33.

With respect to the study reported by the First Chang Declaration, the Declaration describes a study comparing the dissolution rates of:

> Tablet A, containing the ingredients of Formulation A [of Example A-1 of Yada '530], but in an increased amount to correspond to the formulation of Example 1 in the present

> application for comparison purposes. The other one is Tablet B, containing the formulation of Tablet A as the compartment [i.e., the layer] for olmesartan medoxomil in the formulation of Example 1 in the present application. Tablet A was prepared according to the method described in Example A-1 of Yada et al. Tablet B was prepared to a bilayer tablet according to the method of Example 1 in the present application but with no coating[,] for comparison purposes.

First Chang Decl. ¶ 5. The relative formulations of Tablet A and B is reproduced below:

Tablet A

	Formulation A	Tablet A
Olmesartan medoxomil	20 mg	40 mg
Lactose	106 mg	212 mg
L-HPC	20 mg	40 mg
HPC-L	3 mg	6 mg
Avicel	10 mg	20 mg
Magnesium stearate	1 mg	2 mg

Tablet B

	Ingredients	mg
Rosuvastatin-containing layer (mg/tablet)	rosuvastatin calcium	20.80
	lactose monohydrate	119.10
	Prosolv™	42.60
	dibasic calcium phosphate dihydrate	21.80
	crospovidone	10.70
	croscarmellose sodium	6.40
	light anhydrous silicic acid	4.30
	magnesium stearate	4.30
Olmesartan medoxomil-containing layer (mg/tablet	olmesartan medoxomil	40.00
	lactose	212.00
	L-HPC	40.00
	HPC-L	6.00
	Avicel	20.00
	magnesium stearate	2.00

Id. ¶ 6. The First Chang Declaration compares the dissolution rates of Tablets A and B as depicted below:

	Dissolution rate (%)									
Time (mins)	5	10	15	30	45	60	90	120	240	360
Tablet A	15.5 ±1.0	20.4 ±1.6	24.3 ±6.0	36.5 ±1.0	44.4 ±0.5	47.7 ±3.0	51.9 ±2.0	54.9 ±2.0	53.4 ±1.4	56.2 ±2.5
Tablet B	10.5 ±0.3	11.9 ±1.0	16.6 ±0.8	19.9 ±2.9	25.6 ±2.8	31.2 ±1.7	34.6 ±3.7	40.8 ±3.3	46.8 ±1.5	52.5 ±1.6

Id. ¶ 7. The First Chang Declaration states that these values demonstrate that the dissolution rate of Tablet B is significantly lower than the dissolution rate of Tablet A, indicating that olmesartan medoxomil and rosuvastatin, when combined into a single formulation, show a drug interaction or interference in dissolution. *Id.* ¶ 8.

We are not persuaded of the relevance of this demonstration. As an initial matter, Yada '530 expressly teaches formulations combining olmesartan medoxomil and rosuvastatin, and not merely olmesartan medoxomil as the sole active agent. *See* Yada ¶ 39. Furthermore, Staab teaches a layered combination tablet formulation of olmesartan and rosuvastatin, with crospovidone and croscarmellose sodium as disintegrants in the latter layer. Both Yada references teach that L-HPC is a suitable disintegrant for olmesartan medoxomil and Yada '898 teaches use of a concentration of L-HPC within the range recited in claim 33. The First Chang Declaration's conclusion that "olmesartan medoxomil and rosuvastatin, when combined into a single formulation, show a drug interaction or interference in dissolution" when compared to a formulation containing only olmesartan medoxomil, has little relevance when compared to the combined teachings of the cited prior art references, which teach all

the elements of Tablet B in the experiment described in the First Chang Declaration.

Summarizing, we find that the combined references teach or suggest all of the limitations of the claims and that the experiments described in the First Chang Declaration are not relevant in showing that claim 33 is nonobvious over the cited prior art.

Issue 2

Appellant argues that the Examiner erred because a person of ordinary skill in the art would have had no reasonable expectation of success in combining the references. App. Br. 17.

Analysis

Appellant argues that, because biological and pharmacokinetic properties are unpredictable, it would not have been possible for a person of ordinary skill in the art to reasonably expect that simply combining a formulation of Staab with one of the many components in the compositions from the secondary references would have been successful. App. Br. 18. Appellant contends that none of the cited references teach the behavior of both drugs in a single composition. *Id.*

Appellant points to the Second Declaration of Dr. Chang, filed September 10, 2018 (the "Second Chang Declaration") as explaining that, in developing the claimed double-layer tablets, the inventors overcame two previously unknown technical problems involving this specific drug combination. App. Br. 18. These problems were (1) absorption of rosuvastatin in the gastrointestinal membrane was inhibited due to the delay

in dissolution caused by drug-drug interaction between rosuvastatin and olmesartan medoxomil; and (2) the dissolution profile of olmesartan medoxomil, which is pharmaceutically equivalent to the reference (OLMETEC™), was unexpectedly found biologically non-equivalent to the reference tablet, when administered to a patient. *Id.* (citing Second Chang Decl. ¶¶ 5–6). According to Appellant, the inventors invested much time, due to these issues, in the research and development of a formulation that would meet the standards for bioequivalence, while providing the olmesartan medoxomil and rosuvastatin in a double-layered tablet formulation. *Id.*

We do not find this argument persuasive. As an initial matter, Staab teaches a layered formulation that possesses all of the structural limitations of independent claim 33, except for the use of L-HPC as a disintegrant in the olmesartan medoxomil layer at the claimed concentration range. As we have explained, the Yada references teach this limitation.

More importantly, the reasons for the difficulty in arriving at the claimed composition argued by Appellant, are functional reasons related to the olmesartan-rosuvastatin drug interactions and dissolution rates. Neither of these functional properties are recited in claim 33, which is purely structural in its limitations. As such, Appellant's arguments are not commensurate with the scope of the claims, and are not persuasive.

Issue 3

Appellant argues that the Examiner erred in ignoring evidence that the references teach away, and of unexpected results. App. Br. 20.

Analysis

Appellant contends that, according to conventional standards, when developing a formulation that could be regarded as pharmaceutically equivalent to the reference formulation (i.e., OLMETEC™ tablet), the skilled artisan would have been aware that "two requirements should be satisfied in order to meet the pharmaceutical equivalence criteria of the applicable [Korean] Pharmaceutical Affairs Law." *Id.* at 20–21 (quoting Spec. ¶ 76, alteration in original). Specifically, Appellant asserts that:

> [W]here the dissolution rate of a reference formulation (i.e., Olmetec™ tablet) in water for the defined time (i.e., 6 hours) is below 85%, the following two requirements should be satisfied in order to meet the pharmaceutical equivalence criteria of the applicable [Korean] Pharmaceutical Affairs Law: the first requirement that the dissolution rate of the test formulation for 6 hours is located between the dissolution rate of the reference formulation (i.e., Olmetec™ tablet) ± l5% (i.e., 36.13 to 66.13%); and the second requirement that the dissolution rate thereof for 5 minutes (the nearest time to the time for attaining to about ½ (i.e., 25.5%) of the dissolution rate of the reference formulation for 6 hours) is located between the dissolution rate of the reference formulation ± l5% (i.e., 6.30 to 36.30%).

Id. at 21 (quoting Spec. ¶ 76).

Appellant argues that, when formulations meeting these conventional requirements were tested, they did not provide pharmaceutical equivalence to the reference formulation (i.e., OLMETEC™ tablet). *Id.* (citing Spec. ¶¶ 81–82). According to Appellant, the inventors unexpectedly found that the specific tablet claimed causes the tablet to have a dissolution rate over 15% higher than the reference listed tablet, making it pharmaceutically inequivalent and thereby expected to be not bio-equivalent. *Id.*

We are not persuaded. "To be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention." *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Circ. 2014). OLMETEC™, the so-called reference drug, contains only a salt of olmesartan medoxomil as its active agent, whereas the claimed composition is a layered tablet containing olmesartan medoxomil and rosuvastatin as active agents in the respective layers.

The closest prior art in the present case is either Yada '898 or Staab. Staab teaches a layered tablet composition containing olmesartan and rosuvastatin in separate layers. Yada '898 teaches a two drug combination (olmesartan medoxomil and amlodipine besylate) in which the L-HPC content is 20 wt%, which is within the 19–21 wt% range recited in claim 33. Absent any evidence that the claimed composition exhibits unexpected properties compared to those of the layered tablet compositions of Staab, we do not find the Second Chang Declaration probative of non-obviousness.

Furthermore, even standing upon its own merits, we do not find the data presented in the Second Chang Declaration to be probative of nonobviousness. Table 13 of the Second Chang Declaration is reproduced below:

	Disintegrant	Amount (w/w%)	Dissolution rate (5 minutes, %)	Dissolution rate (6 hours, %)
Olmetec™ tablet			21.30	51.13
Example 1	low substituted hydroxypropyl cellulose	19.05	41.73	80.61
Example 4-1		5.00	16.39	61.29
Example 4-2		7.50	38.32	76.98
Example 4-3		60.00	53.39	81.68
Example 4-4		65.00	57.58	82.68

Example 1 tablet containing L-HPC in the amount of 19.05% as claimed, was found pharmaceutically non-equivalent to the reference tablet (OlmetecTM tablet used in Experimental Example 2) because the dissolution rates at 5 mins (41.73%) and 6 hrs. (80.67%) are not within 15% of the dissolution rate of the reference according to the criteria under the KP (or USP). Unexpectedly, however, Example 1 tablet was found bioequivalent to the reference tablet in the bioequivalence test (Experimental Example 3).

In contrast, Example 4-1 tablet containing L-HPC in the amount of 5 wt.% was found pharmaceutically equivalent to the reference tablet because the dissolution rates at 5 mins (16.39%) and 6 hrs. (61.29%) are within 15% of the dissolution rate of the reference, but it was found biologically non-equivalent in the bioequivalence test (Experimental Example 3).

Although we acknowledge Dr. Chang's point that Example 4-1, with 5 wt% L-HPC was found to be pharmaceutically equivalent to the OLMETEC™ reference tablet, we also note that even slightly greater concentrations of L-HPC, e.g., 7.5 wt%, well outside the claimed range of 19–21%, also show results that are pharmaceutically non-equivalent, and comparable to that of the claimed range. In sum, we find the differences between the claimed range and weight percentage values outside of the range to be differences in degree, rather than kind, as is required to demonstrate unexpected results. *See Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004) (holding that unexpected results that are probative of nonobviousness are those that are "different in kind and not merely in degree from the results of the prior art").

Issue 4

Appellant argues that the Examiner erred in failing to properly consider the First and Second Chang Declarations. App. Br. 23. We

disagree. As we have explained, both the First and Second Chang Declaration fail to demonstrate that the properties of the claimed composition are unexpected in comparison with the combined teachings of the cited prior art references, particularly Yada '898 and Staab.

We consequently affirm the Examiner's rejection of the claim 33. Furthermore, because Appellant argues all of the claims together, we similarly affirm the Examiner's rejection of claims 36–42.

CONCLUSION

The Examiner's rejection of claims 33 and 36–42 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).

AFFIRMED

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
33, 36–42	103(a)	Staab, Yada'503, Yada '898, Obara	33, 36–42	