

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HELENA LABORATORIES CORPORATION,

Petitioner,

v.

SEBIA,

Patentee.

CASE IPR2024-00801
PATENT 7,887,686

PETITIONER'S REPLY TO
PATENT OWNER'S PRELIMINARY RESPONSE

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I. The problem and the solution.

The ‘686 patent identifies the problem as a lack of sufficient separation (resolution) of hemoglobin (Hb) components (variants) during capillary electrophoresis (CE) using a zwitterionic buffer (ZB). (Ex. 1001, page 16; Col. 1, lines 7-10.) Adding a flow inhibitor (FI) is said to provide the desired separation. (*Id.*, Abstract, page 1.)

II. Primary (base) and secondary references applicable to all issues.

A “primary” or base reference is that to which features are added or combined, *e.g.*, from other references. *Inline Plastics Corp. v. Lacerta Group, LLC*, 97 F.4th 889, 897 (Fed. Cir. 2024). That designation identifies the reference to be modified by the “secondary” or other references, and where the relevant factual inquiries are otherwise clear, characterizing references as primary and secondary is merely a matter of presentation with no legal significance. *Jodi A. Schwendimann v. Neenah, Inc.*, 82 F.4th 1371, 1384 (Fed. Cir. 2023). There may be multiple “primary” references with each being separately modified by secondary references. *Janssen Pharm Inc. v. Teva Pharm. USA Inc.*, 97 F.4th 915, 928 (Fed. Cir. 2004).

Petitioner’s primary references, Shihabi (Ex. 1011) and Huang (Ex. 1015) were never applied, for any purpose, to any of the claims, yet Patent Owner valiantly attempts to persuade the Board otherwise. That repetitive suggestion in Patent Owner’s Preliminary Response (Paper No. 6) is just incorrect. Petitioner does rely

on one tertiary reference, Camilleri (Ex. 1020) applied to the claims during examination, but here the reliance is for a different proposition.

III. Applicability or inapplicability of the *Becton, Dickinson* factors.

The Board, in *Becton, Dickinson & Co v. B. Braun Melsungen AG*, Case IPR2017001586, Paper 8 at 17 (PTAB Dec. 15, 2017) (Designated Precedential Aug. 2, 2019, as to § III.C.5 ¶ 1), explained a two-part framework in evaluating whether or not to exercise discretion and institute an IPR *when the same or substantially the same prior art or arguments that were presented during examination are presented in the IPR petition*. (Emphasis added) The first part is whether or not “the same or substantially the same prior art or arguments” are being presented. If the answer is affirmative, the second part addresses any Office errors material to patentability. Six non-exclusive factors are presented.

What really happened in *Becton, Dickinson*? As part of the Board’s *Graham v. John Deere Co.*, 383 U.S. 1 (1966) and *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007) evaluation, the Board recognized that the base (primary) reference relied on (Woehr) was, in fact used as a base reference during examination for an obviousness rejection and, in assessing the six factors, the Board declined to institute an IPR based on Woehr. (*Id.*, page 28).

But wait. There is more. The Petitioner (in *Becton, Dickinson*) also relied on a different base reference (Van Heugten), not applied to any claims during

examination, combined with a secondary reference (Tauschinski) that was applied as a secondary reference during examination. That was sufficient for institution of the IPR without any analysis of the six factors (*Id.*, pages 35-39). Thus, the six factor analysis does not appear to be required when there is at least one primary reference not previously applied. Here, Patent Owner seeks to equate the unapplied prior art (Shihabi, Huang) to the prior art “considered but not applied” below (Shihabi). Patent Owner is incorrect.

IV. Factual comparison of Petitioner’s unapplied prior art to the Examiner’s applied prior art.

Technical subject matter	Prior art applied below	Prior art relied on for this IPR
CE of Hb variants using ZB.	None applied to any claim.	Shihabi (Ex. 1011)
CE of Hb variants using ZB.	None applied to any claim.	Huang (Ex. 1015) – not merely cumulative of Shihabi. ¹

¹ Huang discloses use of bis-tris propane as a ZB (Ex. 1015, page 1) -- claimed in the ‘686 patent, claim 15 (Ex. 1001, col. 8, page 19). Shihabi discloses Tris but not bis-tris propane. Huang, but not Shihabi, disclose details of the CE tubes (Ex. 1015, page 1) claimed in the ‘686 patent claims 10 and 11 (Ex. 1001, page 19, col. 7).

Technical subject matter	Prior art applied below	Prior art relied on for this IPR
CE (not of Hb) using ZB and FI.	Camilleri (Ex. 1020) applied as a secondary reference.	Coufal (Ex. 1013). Camilleri (Ex. 1020) ²

Here, each primary reference, Shihabi (Ex. 1011) and Huang (Ex. 1015) discloses Hb variant separation by CE using ZB. No prior art disclosing Hb variant separation by CE using ZB was applied to any claim during examination. That should be dispositive of the *Becton, Dickinson* factors.

The “closest” prior art “known” to the Examiner, Shihabi, a reference teaching CE of Hb variants using a ZB, was never applied against any claim. Not as a primary reference, not as a secondary reference, not as a tertiary reference. Not at all. (Huang, used here as another primary reference, was not of record below.)

The prior art, applied to the claims during examination, are neither the same, nor substantially the same, nor cumulative of, the prior art applied by Petitioner.

V. “Primary” references applied below are not applied here.

² Camilleri is applied as a tertiary reference but for a different technical proposition, namely, tricine as a ZB (Ex. 1020, page 2) -- claimed in the ‘686 patent, claims 15 and 16 (Ex. 1001, col. 8, page 19).

Nouadje *et al* (Ex. 1024) was combined with Keo *et al*, Grover *et al* (Ex. 1021), and Chen *et al* (Ex. 1016) as secondary references in multiple rejections (Ex. 1003, pages 243-256 (first rejection); pages 343-354 (final rejection)). It was then applied as a secondary reference after an RCE was filed. (*Id.*, page 420). The record reflects that Nouadje does not resolve Hb components but only resolves seric proteins in a sample. (*Id.*, page 484)

Sunzeri *et al* (Ex. 1018) was applied both as a 35 USC §102 reference and as a 35 USC §103 reference after the RCE was filed. (Ex. 1013, pages 414-419) But **Sunzeri** did not separate out Hb variants or components but rather, separated only one analyte of interest by first mixing the sample with an analyte binding pair member and then resolving that bound analyte from unbound reagent. (Ex. 1003, pages 458 - 461) (“the detection and separation of more than one analyte-reagent complex is not taught” by Sunzeri)(Quoted from Ex. 1003, page 460, lines 7-9.)

Patent Owner’s assertion about the limitation of Sunzeri was correct.

A Notice of Allowance identified **Sunzeri** as the closest prior art of record, noted that Sunzeri detects a single specific analyte and not multiple Hb variants, (Ex. 1003, page 472), and that Nouadje *et al* did not teach resolution of Hb “constituents” (Ex. 1003, pages 472 - 473).

Having made the successful assertion about the limitation of Sunzeri, Patent Owner should be estopped from arguing that Shihabi and Huang, both of which

separate out multiple Hb variants by CE using ZB, are the same as, similar to, substantially the same as, or cumulative of, Sunzeri.

Both Shihabi and Huang provide at least one “missing link” – separation of Hb variants by CE using a ZB. The evidence supports institution of this IPR.

VI. Secondary references applied here -- only one was applied below and for a different teaching.

Camilleri (Ex. 1020) was relied on during examination for the disclosure of CTAB added to a CE buffer to reverse the charge (Ex. 1003, page 415) and combined with Sunzeri in a second rejection, as using ZB and additives such as 1,4 DAB as an FI. (*Id.*, page 418).³ But Camilleri never expressly states that both a ZB and an FI should be used together. Rather, Camilleri merely provides a “menu” of options: coating the capillary surface dynamically or covalently; additions to the buffer during rinse cycle; increasing buffer concentration; adding salts to the buffer; use of zwitterionic salts instead of ionic salts such as phosphate and borate; use of cationic amines such as DAB and DAP to suppress protein-capillary surface interactions; (*Id.*, page 2) and use of cellulose derivatives, and CTAB for EOF reversal. (*Id.*, page 3). Patent Owner expressly argued below that Camilleri taught “EOF reversal” and

³ Petitioner here did not agree with the Examiner’s statement about Camilleri, rather, Petitioner merely explained what the Examiner had said about Camilleri. Patent Owner, at Paper No. 6 page 22, misreads the Petition.

that was different from a flow inhibitor, (*Id.*, page 461-463, quote from page 461, first paragraph)(emphasis in original).

Here, Petitioner relies on Camilleri as a tertiary reference for a different proposition, namely, a specific ZB (tricine) found in dependent claims 15 and 16 of the '686 patent (Ex. 1001, page 19 and Camilleri, Ex. 1020, page 2). Petitioner's reliance on Camilleri is not redundant

Coufal (Ex. 1013, page 1). teaches a combination of FI and ZB to reduce EOF and thus increase separation. Coufal was not of record during examination.

Patent Owner erroneously attempts to treat Coufal as being relied on for the same reason as Chen and thus argues it is merely cumulative. Patent Owner is incorrect. Petitioner relies on Coufal not only for teaching the combination of FI and ZB as a flow reducer (not a flow reversal) but also for teaching specific ZB concentrations (Ex. 1013, Table 1 and pages 1 and 2) corresponding to the '686 patent claim 6; a buffer pH range greater than that of the primary references and substantially the same as the '686 patent claim 12; the use of a specific pH modifier corresponding to patent claim 18; and Coufal refers to "migration time" (patent claim 23 refers to migration) (Ex. 1001, page 19, col. 7 (claims 6 and 12) and col. 8 (claims 18 and 23)). Coufal is not cumulative to any applied reference.

Chen is not relied on in Petitioner's claim charts. Chen was applied during examination for identification of Hb variants appearing in normal adult blood that

could be separated by CE. (Ex. 1003, pages 254, 350, 351, 352). Patent Owner responded that Chen “merely defines some haemoglobin variants and their separation by CE in the presence of barbituric acids.” (*Id.*, page 309), and that the Chen buffer was barbituric acid, **not zwitterionic buffer**. (*Id.*, pages 405 - 406)(Emphasis added). Patent Owner now argues that Coufal (disclosing a ZB) is redundant to Chen. But, having successfully arguing below that Chen does not disclose a ZB, Patent Owner should be estopped from now urging that Chen’s “barituristic (sic, barbituric) acid” is a ZB. (Paper No. 6, page 22, first full paragraph).

Landers (Ex. 1026) was not applied below. Petitioner argues that Landers and Coufal are redundant. (Paper No. 6, page 25). They are not. Coufal teaches the combination of ZB and FI. Landers teaches putrescine (DAB) as a FI added to a borate buffer (Ex. 1026, page 2), and is relied on here as a tertiary reference for details of a specific FI corresponding to patent claims 5 and 6. (Ex. 1001, page 19, col. 7). There is no redundancy.

VII. Conclusion.

It is not clear that the *Becton, Dickinson* factors are even applicable when Petitioner relies on primary reference not applied to the claims during examination. For the purpose of completeness, however, Petitioner points out the following.

Becton, Dickinson factor (a) as to primary references: Both Shihabi and Huang provide at least one “missing link” – separation of Hb by CE using a ZB. That alone

is a material difference. There are no similarities between primary references which do not disclose separation of Hb into its variants by CE using a ZB (Nouadje, Sunzeri) and those unapplied references that do disclose separation of Hb by CE using a ZB. (Shihabi Huang) The evidence relative to factor (a) supports institution of this IPR.

Becton, Dickinson factor (b) as to primary references: Again, both Shihabi and Huang provide at least one “missing link” – separation of Hb variants by CE using a ZB. Neither is cumulative to any prior art applied during examination. The evidence relative to factor (b) supports institution of this IPR.

Becton, Dickinson factors (a) and (b) compared to secondary and tertiary references applied during examination: (i) as to Camilleri, there are material differences because Camilleri is applied here for a different teaching; (ii) as to Coufal, it is not cumulative as indicated above in Section VI; and (iii) as to Landers, it was not applied below, does not relate to ZB, and is applied here for a different teaching. The evidence for these factors (a) and (b) relative to secondary and tertiary references supports institution of this IPR.

Becton, Dickinson factor (c): Camilleri is the only prior art used as a basis for rejection (incorrectly according to Patent Owner because of flow reversal) that is applied here albeit for a different reaching. The evidence relative to factor (c) supports institution of this IPR.

Becton, Dickinson factor (d): There is no overlap between arguments made by the Examiner and arguments made here by Petitioner. The rejections/arguments by the Examiner are inapplicable to the primary references relied on by Petitioner. The evidence relative to factor (d) supports institution of this IPR.

Becton, Dickinson factor (e): The Examiner erred when identifying Sunzeri as the closest prior art because it did not separate Hb variants at all. The Examiner erred in the interpretation of Sunzeri as pointed out by Patent Owner below. The Examiner erred in the interpretation of Nouadje as pointed out by Patent Owner below. Since Shihabi did disclose Hb variant separation by CE using ZB, as pointed out in the ‘686 patent (Ex. 1001, page 16, col. 1, line 65 through col. 2, line 1) the Examiner erred in not identifying Shihabi as the closest prior art. The evidence relative to factor (e) supports institution of this IPR.

Becton, Dickinson factor (f): Again, both Shihabi and Huang provide at least one “missing link” and neither is cumulative to any prior art applied during examination. They constitute additional evidence relative to factor (f) and support institution of this IPR.

For each of these reasons, as well as the reasons in the Petition, the Board should exercise its discretion and institute this IPR.

August 16, 2024.

Respectfully submitted,

/JIS/

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CERTIFICATE OF SERVICE

The undersigned certifies service on the Patent Owner, under 37 C.F.R. § 42.6(e) by electronic (e-mail) delivery of a true copy of the foregoing to the attorneys of record for Patent Owner:

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