

## REMARKS

Claims 1, 4-13, 15-21, and 23-30 are pending in this application.

### Claim Objections

Claims 18-19, 24, and 26 are objected to.

### Rejections for Lack of Written Description and New Matter

Claims 1, 4-12, 15, 23, 25, and 28-30 are rejected under 35 U.S.C. § 112, first paragraph, for lack of written description and new matter.

### Rejection for Indefiniteness

Claim 24 is rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness.

### Rejections for Anticipation

Claims 18-21 and 24 are rejected under 35 U.S.C. § 102(b) for anticipation by Devarajan et al. (U.S. Patent Application Publication No. 2004/0219603 A1; hereinafter “Devarajan 1”) as evidenced by Mishra et al. (Lancet 365:1231-1238, 2005; hereinafter “Mishra”).

### Rejections for Obviousness

Claims 1, 4-12, 15-16, and 28-30 are rejected under 35 U.S.C. § 103(a) for obviousness over Devarajan 1 in view of Holvoet et al. (U.S. Patent No. 6,309,888; hereinafter “Holvoet”), Alocilja et al. (U.S. Patent No. 6,537,802; hereinafter “Alocilja”), Wu et al. (Clinica Chimica Acta 272:11-21, 1998; hereinafter “Wu”), Buechler et al. (U.S. Patent No. 5,939,272; hereinafter “Buechler”), Fraser (Chap. 4 in Biological Variation: From Principles to Practice, AAAC Press, pp. 91-116, 2001; hereinafter “Fraser”), Elneihoum et al. (Atherosclerosis 131:79-84, 1997; hereinafter “Elneihoum”), and Forsblad et al. (Int. Angiol. 21:173-179, 2002; hereinafter “Forsblad”). Claim 17 is rejected under 35 U.S.C. § 103(a) for obviousness over Devarajan 1 in view of Holvoet, Alocilja, Wu, Buechler, Fraser, Elneihoum, and Forsblad, and further in view of Devarajan et al. (U.S. Patent Application Publication No. 2005/0272101 A1; hereinafter

“Devarajan 2”). Claims 13 is rejected under 35 U.S.C. § 103(a) for obviousness over Devarajan 1 in view of Holvoet, Alocilja, Wu, Buechler, Fraser, Elneihoum, Forsblad, Rose et al. (U.S. Patent No. 6,986,995; hereinafter “Rose”), and Clark et al. (U.S. Patent No. 5,273,961; hereinafter “Clark”). Claim 23 is rejected under 35 U.S.C. § 103(a) for obviousness over Devarajan 1. Claims 18-21 and 23-27 are rejected under 35 U.S.C. § 103(a) for obviousness over Devarajan 1 in view of Nelson et al. (U.S. Patent No. 6,762,032; hereinafter “Nelson”). Claims 1, 4-12, 15-21, and 23-30 are provisionally rejected for obviousness-type double patenting over claims 1-14 of U.S. Serial No. 12/375,585 and over claims 1-15 and 16-17 of U.S. Serial No. 12/302,931 in view of Devarajan 1, Holvoet, Alocilja, and Wu or, in the alternative, in view of Devarajan 1, Holvoet, Alocilja, Wu, Buechler, Fraser, Elneihoum, and Forsblad. Finally, claim 13 is provisionally rejected over claims 1-14 of U.S. Serial No. 12/375,585 in view of Devarajan 1, Rose, and Clark, and over claims 1-15 and 16-17 of U.S. Serial No. 12/302,931 in view of Devarajan 1, Holvoet, Alocilja, and Wu or, in the alternative, in view of Devarajan 1, Holvoet, Alocilja, Wu, Buechler, Fraser, Elneihoum, Forsblad, Rose, and Clark.

By this reply, Applicant cancels claims 16-21 and 23-29, amends claim 1, and addresses each of the objections and rejections.

#### Support for the Amendment

Claim 1 has been amended to incorporate the limitation of prior claims 16 and 17. No new matter is added by the amendment.

#### Personal Interview

Applicant’s representatives, Susanne Høiberg, Pernille Gojkovic, Kristina Bieker-Brady, and Todd Armstrong, as well as the inventors, Lars Otto Uttenthal and Kristian Bangert, wish to thank Examiner Foster and her supervisor, Mark Shibuya, for the courtesy of an in person interview on February 2, 2011. The written description, new matter, clarity, novelty, obviousness, and obviousness-type double patenting rejections detailed in the final Office Action dated December 8, 2011, were discussed. The substance of the interview is discussed herein.

### Objections to the Claims

The objections raised against claims 18-19, 24, and 26 have been rendered moot by the cancellation of these claims.

### Rejections under 35 U.S.C. § 112, first paragraph

The Office rejects claims 1, 4-12, 15, 23, 25, and 28-30 under 35 U.S.C. § 112, first paragraph, for lack of written description and new matter. Applicant wishes to thank the Examiner for her suggestion to amend claim 1 to specify that the bodily fluid is urine, plasma, or serum in response to this rejection. Claim 1 has been so amended. Thus, the rejection of claim 1 has been overcome. The rejections of the remaining claims has been rendered moot by the amendment of claim 1 from which claims 4-12, 15, and 30 depend and the cancellation of claims 23, 25, and 28-29.

### Rejections under 35 U.S.C. § 112, second paragraph

The Office rejects claim 24 under 35 U.S.C. § 112, second paragraph. Claim 24 has been cancelled, which renders the rejection moot.

### Rejection under 35 U.S.C. § 102(b)

The Office rejects claims 18-21 and 24 under 35 U.S.C. § 102(b). Claims 18-21 and 24 have been cancelled, rendering the rejection moot.

### Rejections under 35 U.S.C. 103(a)

#### ***A. The Rejection of Claims 1, 4-12, 15-16, and 28-30***

The Office rejects claims 1, 4-12, 15-16, and 28-30 under 35 U.S.C. 103(a) for obviousness over Devarajan 1 in view of Holvoet, Alocilja, Wu, Buechler, Fraser, Elneihoum, and Forsblad. Claims 16, 28, and 29 have been cancelled. Applicant provides the following remarks with respect to claims 1, 4-12, 15, and 30.

## **I. The Present Inventors were the First to Identify a Cutoff Value for NGAL that Discriminates Between Renal Disorders and Non-Renal Disorders**

As was discussed during the personal interview, the present inventors were the first to recognize that a cutoff value of 250 ng/mL or greater for NGAL could be used to discriminate, in a human being, between a renal disorder and a non-renal disorder (i.e. a condition that does not affect the kidney). The present inventors recognized that NGAL levels may be raised in humans due to non-renal conditions, such as, e.g., inflammation, infection, and cancer, and thus separating these non-renal disorder patients from those patients with a renal disorder. Applicant's claimed diagnostic method is beneficial for guiding clinical decision-making, as the onset of renal disorders is otherwise mostly silent and the cause of high mortality.

## **II. Devarajan 1 Does Not Teach or Suggest Cutoff Levels for NGAL**

The Office states that Devarajan 1 teaches that increases in urinary NGAL levels are indicative of ischemic renal injury (Office Action, p. 11), yet acknowledges that Devarajan 1 “does not specifically teach the use of cutoff values, or in particular of a cutoff value of 250 **ng/mL or higher**” (Office Action, p. 12; emphasis in original). In fact, there is no evidence in Devarajan 1 of NGAL levels above approximately 160 ng/mg creatinine (see Figure 16), and thus Devarajan 1 provides no reason to assign a cutoff value above this concentration in order to discriminate between a human having a renal disorder and one having a non-renal disorder.

Furthermore, Devarajan 1 provides no motivation to set a cutoff value above approximately 160 ng/mg creatinine because to do so would exclude all of those patients presumptively identified in Devarajan 1 as having a renal disorder (“If the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification.” See M.P.E.P. § 2143.01(V), *citing In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984). *See also DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314 (Fed. Cir. 2009); *Icon Health & Fitness, Inc.*, 496 F.3d 1374, 1382 (Fed. Cir. 2007). Thus, contrary to the Office's conclusion, one of skill in the art would not look beyond the disclosure of Devarajan 1 for a cutoff value of 250 ng/mL or

greater for discriminating between a renal disorder and a non-renal disorder in a patient.

### **III. Holvoet, Alocilja, Wu, Buechler, Fraser, Elneihoum, and Forsblad Fail to Cure the Deficiencies of Devarajan 1**

To cure the deficiencies of Devarajan 1, the Office relies on Holvoet, Alocilja, Wu, Buechler, and Fraser as evidence that “it was well known in the art at the time of the instant invention to use cutoff values in clinical assays as a means of comparison in order to objectively interpret laboratory results...[, and] cut-off concentrations that are at the upper limit of normal may be selected [for this purpose]” (Office Action, pp. 12-13). The Office further relies on Elneihoum for its teaching that plasma levels of NGAL are correlated with age as well as hypertension in women, and Forsblad for its disclosure that NGAL plasma levels in an elderly population ranges from 53 ng/mL to 263 ng/mL or from 67 ng/mL to 241 ng/mL in patients without or with cardiovascular disease, respectively (Office Action, p. 19).

None of Holvoet, Alocilja, Wu, Buechler, or Fraser relates to NGAL or to discriminating patients with renal disorders from those with non-renal disorders, and neither Elneihoum nor Forsblad relates to the use of a cutoff value for NGAL, much less detecting a renal disorder in a patient. Thus, even if combined with Devarajan 1, none of Holvoet, Alocilja, Wu, Buechler, Fraser, Elneihoum, or Forsblad provides any motivation to use a cutoff value of 250 ng/mL or greater to discriminate between a renal disorder and a non-renal disorder in a human, nor any reasonable expectation of success in using a cutoff value of 250 ng/mL or greater to achieve this discrimination. Thus, the Office has failed to establish a *prima facie* case of obviousness for the claimed invention based on the combination of Devarajan 1, Holvoet, Alocilja, Wu, Buechler, Fraser, Elneihoum, and Forsblad.

Furthermore, the Office appears to support its obviousness rejection against present claims 1, 4-12, 15, and 30 by simply picking and choosing information from each of the cited publications only to the extent necessary to assemble the component parts of the rejected claims and has not considered the cited publications as a whole. When evaluating claims for obviousness, “the prior art as a whole must be considered. The teachings are to be viewed as they would have been viewed by one of ordinary skill.” *In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir.

1986). “It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.” *In re Wesslau*, 353 F.2d 238, 241 (CCPA 1965).

The facts of the present case are similar to those of *In re Hedges*. The claims at issue in *Hedges* were directed to a process of sulfonating diphenyl sulfone by “contacting diphenyl sulfone in its molten state with...sulfur trioxide in the absence of water or a solvent, thereby sulfonating the sulfone in high yields without forming by-product sulfuric acid.” The process occurs at a reaction temperature above 127°C, which is the temperature at which diphenyl sulfone is in its molten state. The Examiner rejected the claims for obviousness over a primary publication, Felix (U.S. Patent No. 2,010,754), which “shows the sulfonation of aryl sulfones with sulfur trioxide in the form of fuming sulphuric acid. Sulfonation is carried out at 5-10°C, after which the temperature exothermically rises to 30°C before it is lowered to room temperature” (*In re Hedges*, 783 at 1039). The Examiner held that because Felix “shows no upper limit to the temperature of the reaction...[,] determining the optimum temperature is a matter of ‘routine experimentation’” (*Id.* at 1040). On appeal, the Board affirmed the obviousness rejection by combining Felix with three additional references Mark (U.S. Patent No. 3,948,851), British Patent No. 820,659, and certain pages of a book by Gilbert entitled “Sulfonation and Related Reactions”).

Before the Federal Circuit, the PTO Solicitor (“PTO”) argued that evidence in support of the obviousness rejection was found in Felix and in the three additional cited references, which show an “open-ended teaching of the use of higher temperatures, such as over 127°C, for this reaction” (*Id.* at 1040). Hedges argued that “the low temperatures shown by Felix defeat any prima facie case of obviousness of the reaction at above 127°C...[and] that, viewing the references as a whole, it would not have been obvious to operate in the molten state at high temperatures” (*Id.* at 1039). The Federal Circuit resoundingly agreed with Hedges, stating that the “[t]he plain reading of Felix is contrary to the PTO position and...appears to be an extremely strained interpretation of [Felix] which could be made only by hindsight” (*Id.* at 1040). Furthermore, the PTO’s reading of the three additional cited references as teaching a higher

reaction temperature “is not a reasonable one...[because] [n]o reference suggests that diphenyl sulfone may advantageously be reacted in the molten state with sulfur trioxide” (*Id.* at 1041).

The Federal Circuit stated:

We agree with Hedges that the prior art as a whole must be considered. The teachings are to be viewed as they would have been viewed by one of ordinary skill... “It is impermissible within the framework of section 103 to pick and chose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.”

(*Id.* at 1041), citing *In re Wesslau*, F.2d 238, 241 (CCPA 1965)).

As in *Hedges*, where the PTO argued that one of skill in the art would increase the reaction temperature of the reaction described by Felix by routine optimization because Felix shows no upper limit to the reaction temperature, the Office in this case relies on an extremely strained interpretation of Devarajan 1 in drawing its conclusion that because “Devarajan [1] make[s] clear that *increases* in NGAL are indicative of renal disorders...[,] it would have been obvious to arrive at the claimed invention by optimizing the cutoff value of NGAL in order to achieve a desired sensitivity and/or specificity depending on the goal of the screening procedure” (Office Action, pp. 11 and 16). As is acknowledged by the Office, Devarajan 1 fails to teach or suggest any cutoff value for NGAL, much less a cutoff value of 250 ng/mL or greater (Office Action, p. 12). Therefore, just as in *Hedges*, where the PTO combined three additional publications as evidence that one of skill in the art would increase the temperature of the sulfonation reaction, the Office seeks to cure the deficiencies of Devarajan 1 by relying on seven additional publications, namely Holvoet, Alocilja, Wu, Buechler, Fraser, Elneihoum, and Forsbald, to support its conclusion that one of skill in the art would select a cutoff value for NGAL of 250 ng/mL or greater to yield the claimed method. Yet, as was the case in *Hedges*, when these additional publications are considered as a whole, it is very apparent that no reference suggests that a cutoff value for NGAL of 250 ng/mL or greater may advantageously be selected to discriminate, in a patient, between a renal disorder and a non-renal disorder (“[The cited publications] cannot fairly be given the predictive virtues attributed to [them] by the [Office]”; *In re Hedges* (783 at 1041)). Thus, as in *Hedges*, the present case is a clear example of the Office picking and choosing from the cited references only so much as will

support its obviousness rejection to the exclusion of other parts necessary to the full appreciation of what the references fairly suggest to one of ordinary skill in the art, which is impermissible within the framework of 35 U.S.C. § 103 (*Id.* at 1041).

For example, the Office states that Holvoet teaches that a pre-determined cutoff level for an analyte can be used to distinguish between patients having a disease and those that do not (Office Action, p. 12). The Office's conclusion based on Holvoet presupposes that a cutoff level is applicable to any given analyte. Yet not all analytes / markers are useful in the context of a cutoff value. In particular, Fraser, which is cited by the Office for its disclosure that many analytes change over the lifespan of an individual or depending on sex, states in relation to serum creatinine that “[w]hen we examined the variability of serum creatinine over time in a few men and a few women..., we found that individuals really are individuals. This limits the utility of conventional reference values” (p. 102; emphasis added). Thus, Fraser clearly indicates that one skilled in the art would not necessarily expect reference or cutoff values to be applicable to all analytes, and certainly provides no motivation or reasonable expectation of success in identifying a cutoff value for NGAL in the context of renal disorders.

In addition, the Office cites Wu for the proposition that “[i]t was known to employ cutoff concentrations corresponding to the upper limit of normal” (Office Action, p. 18, 2<sup>nd</sup> bullet). This particular conclusion is based on a citation from Wu that is taken out of context. Wu, with respect to the specific cardiac markers troponin T and troponin I, states that “[i]n blood of normal individuals, levels of these proteins are essentially absent suggesting there is little turnover of myocardial tissue. Therefore it is appropriate to set the cut-off concentration at the upper limit of normal” (Wu, p. 15; emphasis added). The cardiac markers and the context of their use discussed in Wu are inapplicable to the method of present claims 1, 4-12, 15, and 30, which is directed to the discrimination between a renal disorder and non-renal disorder in a human using NGAL. Unlike the specific cardiac markers discussed in Wu, NGAL is, as stated in the present application, present in bodily fluids in the absence of any renal disorder (see, e.g., p. 3, lines 17-31), and it may be present in significant amounts in this patient population (see Table 2 of the present specification). Unlike the situation in Wu, NGAL expression is not “essentially absent” in patients with a non-renal disorder. Thus, the Office's extrapolation of Wu's conclusion with



respect to specific cardiac markers to NGAL and renal disorders has no basis in the prior art and is further evidence of the Office's improper choosing of particular statements within the reference (*In re Wesslau, supra*).

Still yet, the Office relies on Elneihoum as evidence of an elderly patient population with raised NGAL levels and, in particular, on Forsblad as evidence that NGAL plasma levels in an elderly population without cardiovascular disease ranges from 53 ng/mL to 263 ng/mL. Neither of these publications provides any motivation to use 263 ng/mL as a cutoff value for discriminating between a renal disorder and a non-renal disorder in a human, as is suggested by the Office, much less any reasonable expectation that such a cutoff value would provide this discrimination. In fact, neither Elneihoum nor Forsblad states that the values given for NGAL are "normal." Indeed, there is no indication in Elneihoum or Forsblad as to whether the study population is otherwise healthy, much less whether the specific individual patient with an NGAL concentration of 263 ng/mL might or might not be suffering from a renal disorder. Forsblad is silent on this point. Thus, the Office's conclusion that "it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention by employing cutoff values of 263 ng/mL or higher when performing the methods of detecting renal injury of Devarajan [1]... in elderly patients" is a mere conclusory statement without any support whatsoever in the cited publications (The Office bears the initial burden of establishing a *prima facie* case of obviousness based upon the prior art. *In re Fritch*, 972 F.2d 1260, 1265, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). "[T]here must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). Mere conclusory statements will not suffice. M.P.E.P. § 2143.01(IV)).

Furthermore, in *KSR Int'l v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007), the Supreme Court noted that it is only when one of ordinary skill in the art is confronted with "a *finite* number of identified, predictable solutions" to a problem and pursues "the known options within his or her technical grasp" that the resulting discovery may have been obvious (emphasis added). The Federal Circuit has explained that this "finite number" must be a "small or easily traversed" group of alternatives. *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008) (holding that the claimed compound was not obvious where the prior art did not

present “a finite, and in the context of the prior art, small or easily traversed” number of potential starting compounds, and there was no apparent reason for selecting a particular starting compound from among a number of unpredictable alternatives). If, on the other hand, one of skill in the art would have had to select from “numerous possible choices” with the prior art providing “either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful,” the claimed invention would not have been obvious. *Proctor & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 996-97 (Fed. Cir. 2009) (quoting *In re O’Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)). This is because obviousness is not established when one “merely throws metaphorical darts at a board filled with combinatorial prior art possibilities.” *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009).

Here, the Office has failed to show that the selection of a cutoff value of 250 ng/mL or greater for NGAL in the context of the method of present claims 1, 4-12, 15, and 30 is based on a *finite* number of identified, predictable solutions” to the problem of discriminating in a human between a renal disorder and a non-renal disorder. None of the publications cited by the Office provide any teaching or suggestion of a cutoff value for NGAL, much less any indication as to which cutoff value for NGAL would achieve success.

Thus, it is clear from the above examples that the Office has not considered the cited publications as would one of skill in the art, nor has the Office shown that the selection of Applicant’s cutoff value for NGAL of 250 ng/mL or greater is based on a *finite* number of predictable solutions identified in the cited publications. Instead, the Office relies only on those parts of the cited publications that it deems to support the present obviousness rejection to the exclusion of parts that clearly do not support the Office’s position. This is clearly impermissible (*In re Hedges, supra*). When properly viewed, the publications cited by the Office fail to support the rejection of claims 1, 4-12, 15, and 30 for obviousness, and thus the obviousness rejection should be withdrawn.

#### **IV. The Office Must Consider All Evidence of Nonobviousness, Including Evidence that Teaches Away from the Claim Invention**

The Office has also failed to acknowledge evidence in the prior art that does not support

its obviousness rejection. This is most evident in the Office’s exclusion of information from Devarajan 2 that is directly contrary to the Office’s conclusions regarding the obviousness of the present claims. In particular, Devarajan 2 explicitly states that “[a] ROC curve for the 2-hour urine NGAL revealed an area under the curve of 0.998, and a sensitivity of 1.00 and specificity of 0.98 **for a cutoff value of 50 ng/ml**” (¶ [0061]; emphasis added). Thus, the Office needed only to review Devarajan 2 to find an explicit teaching of 50 ng/mL as the cutoff value for NGAL when diagnosing renal disorders, which is considerably lower than Applicant’s claimed 250 ng/mL or greater cutoff value. Furthermore, Devarajan 2 specifically states that **a lower cutoff value for NGAL of 25 ng/mL** “yields outstanding sensitivity and specificity” when measured in urine and is “optimal” when measured in serum (see ¶ [0075]). Moreover, Devarajan 2 shows significant decreases in both sensitivity and specificity when the cutoff value of NGAL is increased to 80 and 100 ng/mL, respectively (see Table 2 on page 9). Thus, Devarajan 2 clearly teaches away from the use of a cutoff value for NGAL of greater than 50 ng/mL, much less a cutoff of 250 ng/mL, and teaches that increasing the cutoff value for NGAL above 50 ng/mL reduces the sensitivity and specificity for diagnosing acute renal failure, whether in urine or serum. This is powerful evidence of nonobviousness. *See Crocs, Inc. v. U.S. Int’l Trade Comm’n.*, 598 F.3d 1294 (Fed. Cir. 2010); *Depuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314 (Fed. Cir. 2009); *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552, (Fed.Cir. 1983), cert. denied, 469 U.S. 851, 105 S.Ct. 172, 83 L.Ed.2d 107 (1984), citing *United States v. Adams*, 383 U.S. 39, 86 S.Ct. 708, 15 L.Ed.2d 572 (1966).

The Office cannot merely point to disparate references (e.g., Holvoet, Alocilja, Wu, Buechler, Fraser, Elneihoum, and Forsbald) to identify the individual claim elements in the prior art in order to establish the obviousness of claims 1, 4-12, 15, and 30, especially here where the prior art (Devarajan 2) teaches away from the claimed use of a cutoff value of 250 ng/mL or greater for NGAL and towards significantly lower cutoff value for NGAL of 50 ng/mL and 25 ng/mL. Based on Devarajan 2, the ordinarily skilled artisan would have been deterred from combining the cited references in the manner suggested by the Office.

In addition, the Office, citing *In re Aller*, 220 F.2d 454, 456 (CCPA 1955), states that “[w]here the general conditions of a claim are disclosed in the prior art, it is not inventive to

discover the optimum or workable ranges by routine experimentation” (Office Action, p. 16). *In re Aller* is clearly distinguished from the present facts.

Both the *Aller* method and the prior art Hock and Lang method to which it was compared were directed to the production of the same composition, phenol, and differed only with respect to the sulphuric acid concentration used (25 to 70% vs. 10%) and the reaction temperature (40 to 80°C vs. 100°C). The question put to the *Aller* court was whether the modifications that the *Aller* Inventors made to the Hock and Lang method would have been obvious to one skilled in the art.

The *Aller* Inventors argued that the modifications to the prior art Hock and Lang method resulted in a greater yield of phenol and acetone and a decreased reaction time. The *Aller* court, finding no substantial difference between the *Aller* method and the Hock and Lang method, stated:

In analyzing these improved results, one is not struck by any difference in kind attributable to appellants’ process – logically the improvements could flow equally well from changes in degree resulting from routine variation in temperature or acid concentration. At the least efficient conditions reported by appellants, the improvement is but a few percentage points different from the results reported by the reference. At the most efficient conditions, the improvement is still within the range of variation one might expect to result from changes in reaction conditions. There is no temperature range or acid concentration range that can really be termed “critical.”...Appellants have not shown anything “critical” about their process, unless lower temperatures and higher acidity generally are critical. (*Id* at 457.)

Thus, *In re Aller* involved a situation in which both the *Aller* method and the prior art Hock and Lang method produced the same product with seemingly little or no improvement in the product or the method used to make the product. The *Aller* test, therefore, is whether a claimed process or composition is different in kind and not merely in degree and whether the criticality of the claimed ranges has been shown.

In this case, Applicant’s selection of a cutoff value for NGAL of 250 ng/mL or greater for use in discriminating, in a patient, between a renal disorder and a non-renal disorder is an improvement that does not flow from any of the cited publications, as none of the cited publications, whether considered singly or in combination, teaches or suggests such a cutoff

value. The data presented in Table 2 of the present specification clearly show that a cutoff value for NGAL of 250 ng/mL or greater distinguishes patients having a renal disorder from those patients having a non-renal disorder.

Furthermore, as is discussed above, the prior art (Devarajan 2) directs the skilled artisan away from Applicant's claimed cutoff value for NGAL and to cutoff values considerably lower (i.e., 50 ng/mL and 25 ng/mL), and thus the invention of present claims 1, 4-12, 15, and 30 cannot be the result of routine optimization because the cited prior art provides no basis for one of skill in the art to increase the cutoff amount for NGAL (*see In re Hedges, supra*).

Finally, only the present Applicant recognized that a cutoff value for NGAL of 250 ng/mL or greater could be used to discriminate, in a patient, between a renal and a non-renal disorder. It was only after publication of Devarajan 1 and 2 that the Devarajan inventors realized that their selection of a cutoff value of 50 ng/mL or less was based on data that was later deemed "not as robust" when they found approximately 25-fold higher NGAL levels (median 80 ng/mL) in healthy children (see Wheeler et al., Crit. Care Med. 36:1297-1300, 2008, p. 1300, right column; a copy is provided) than those in Devarajan 2. Thus, Applicant's cutoff value for NGAL of 250 g/mL or greater is not only **not** taught or suggested by the publications cited by the Office, but has been shown by the present inventors' own data to be critical for discriminating, in a patient, between a renal disorder and a non-renal disorder (see Table 2 of Applicant's specification). This conclusion is further supported by the Devarajan inventors' own admission that their data utilized for the conclusions in Devarajan 2 is "not as robust" as their later data showing much higher levels of NGAL in patients (see Wheeler, *supra*).

Thus, for all of the reasons given above, the invention of present claims 1, 4-12, 15, and 30 is more than the result of routine optimization. Accordingly, the rejection of claims 1, 4-12, 15, and 30 for obviousness should be withdrawn.

#### **V. The Present Invention also Applies to Pediatric Patients**

During the personal interview, the Office stated that one of skill in the art would read Devarajan 2 as teaching or suggesting the selection of a cutoff value for NGAL of 50 ng/mL or less for use in pediatric patients only, and thus that the presently claimed cutoff value for NGAL

of 250 ng/mL or greater would not apply to pediatric patients. Applicant respectfully disagrees.

The conclusions of Devarajan 2 are not limited to pediatric patients. Devarajan 2 states:

Ischemic renal injury has also been associated with open heart surgery, due to the brief interruption in blood flow that is inherent in this procedure. The number of open heart surgeries performed annually can be estimated. In any moderately busy adult hospital, approximately 500 such operations are performed every year. Given that there are at least 400 such moderately busy hospitals in the United States alone, one can conservatively estimate that 200,000 open heart surgeries are performed every year. Again, serial NGAL measurements would be invaluable in these patients, and would represent the standard of care.

(Devarajan 2, ¶ [0060]). In addition, Devarajan 2 states that “[u]rine and blood were also obtained from healthy adult volunteers for establishment of normal NGAL values” (¶ [0062]) and that urine and serum NGAL levels were consistently low in healthy adult volunteers (¶¶ [0072] and [0073]). Thus, Devarajan 2 clearly envisions the application of its cutoff value for NGAL of 50 ng/mL or less to adult patients, as the value of NGAL in adult patients was also assayed to identify a “normal NGAL value.” Accordingly, contrary to the Office’s conclusion, one of skill in the art would not limit its reading of Devarajan 2 to pediatric patients.

Furthermore, Wheeler et al. (*supra*) clearly shows that, even in pediatric patients, the levels of NGAL are much higher than those referenced in Devarajan 1 and 2. Wheeler et al. states that “[i]n the current study, serum NGAL in healthy children was much higher (median 80 ng/mL, IQR 55.5-85.5 ng/mL)” (p. 1300). Thus, the evidence of record shows that the invention of present claims 1, 4-12, 15, and 30 is not appropriately limited to adult patients.

## **VI. Conclusion**

For all the reasons given above, the Office has failed to establish a *prima facie* case of obviousness against claims 1, 4-12, 15, and 30. Thus, the rejection of claims 1, 4-12, 15, and 30 for obviousness over the combination of Devarajan 1, Holvoet, Alocilja, Wu, Buechler, Fraser, Elneihoum, and Forsblad should be withdrawn.

***B. The Rejection of Claim 13***

The Office also rejects claim 13 under 35 U.S.C. § 103(a) for obviousness over Devarajan 1 in view of Holvoet, Alocilja, Wu, Buechler, Fraser, Elneihoum, Forsblad, Rose, and Clark. For the reasons discussed above, none of Devarajan 1, Holvoet, Alocilja, Wu, Buechler, Fraser, Elneihoum, or Forsblad, either singly or in combination, teaches or suggests the method of present independent claim 1, from which claim 13, depends. Rose and Clark fail to remedy the deficiencies of Devarajan 1, Holvoet, Alocilja, Wu, Buechler, Fraser, Elneihoum, and Forsblad.

The Office states that “[t]he teachings of Rose et al. therefore indicate that it was known in the prior art to employ multiple cutoff values in clinical diagnostic methods, in order to not only detect the presence of disease but also detect the presence of significant disease” (Office Action, p. 25), while “Clark et al. teaches that severe renal injury or severe acute renal failure (ARF) requires therapy by dialysis” (Office Action, p. 25). Applicant respectfully traverses this rejection.

Neither Rose nor Clark references cutoff values for NGAL, much less the use of an NGAL concentration of 250 ng/mL or greater as a cutoff value to discriminate, in a human patient, between a renal disorder and a non-renal disorder. Thus, Rose and Clark, whether considered alone or in combination with Devarajan 1, Holvoet, Alocilja, Wu, Buechler, Fraser, Elneihoum, and Forsblad, fail to teach or suggest the method of present independent claim 1, from which claim 13 depends. Furthermore, none of Devarajan 1, Holvoet, Alocilja, Wu, Buechler, Fraser, Elneihoum, Forsblad, Rose, or Clark, whether considered singly or in combination, teaches or suggests the use of a second NGAL cutoff value of between 1,000 ng/mL and 3,000 ng/mL to indicate that a human being has a degree of renal disorder that requires or will require treatment by dialysis when their NGAL level is determined to be equal to or greater than the second cutoff value. The Office states:

it would have been obvious to employ the known technique of Rose et al. of using a second cutoff value to improve the similar methods of Devarajan et al. and others...so that renal injury could be not only detected but its severity assessed.

Furthermore, in light of the teachings of Clark et al. that severe acute renal failure or severe renal injury were known to require treatment by hemodialysis, the ordinary artisan would have found it further obvious to conclude that patients

determined to have more severe renal injury would be highly likely to require treatment by dialysis.

(Office Action, p. 26.) The Office's conclusion that one of skill in the art would employ a second NGAL cutoff value of between 1,000 ng/mL and 3,000 ng/mL to indicate the need for dialysis is not supported by the cited publications.

From a scientific or clinical point of view, it can be said that while a dialysis requirement is in general terms an indication of the "severity" of renal failure, it is not a simple matter of deterioration of a single "severity" parameter, but a question of deterioration of individual aspects of renal function that are essential for the maintenance of life. An example of such an individual function is the ability to maintain serum potassium levels below the high level that causes cardiac arrest. Examples of other individual functions that are less important for the maintenance of life are urea and creatinine excretion; these substances can be allowed to rise to very high levels in the blood without prejudicing vital functions. Thus for an individual patient with a moderate degree of renal failure an increase in the severity of that particular type of renal failure may not necessarily lead to a dialysis requirement. If the increasing severity happens to spare those functions that are necessary for preserving life, dialysis may not in fact become necessary. Therefore, it is not obvious that a more severe degree of renal failure or a higher NGAL level will necessarily be associated with a dialysis requirement. It was only the inventors' empirical finding, which was not known from the cited prior art, that higher levels of NGAL are in fact associated with a dialysis requirement.

Contrary to the Office's conclusion, none of the cited publications teaches or suggests how the skilled artisan may ascertain the point at which a patient suffering from a renal disorder is in need of dialysis, much less whether a second cutoff value of any biomarker, let alone NGAL, could be used to make this determination. Only the present inventors have established that a second NGAL cutoff value of between 1,000 ng/mL and 3,000 ng/mL can be used to determine the need for dialysis in such patients. The rejection of claim 13 for obviousness over Devarajan, Holvoet, Alocilja, Wu, Buechler, Fraser, Elneihoum, and Forsblad in view of Rose and Clark should be withdrawn.



***C. The Rejection of Claim 17***

Claim 17 is rejected under 35 U.S.C. § 103(a) for obviousness over Devarajan 1 in view of Holvoet, Alocilja, Wu, Buechler, Fraser, Elneihoum, and Forsblad, and further in view of Devarajan 2 is moot in view of the cancellation of claim 17.

***D. The Rejection of Claim 23***

The Office also rejects claim 23 under 35 U.S.C. § 103(a) for obviousness over Devarajan 1 in view of Nelson. Claim 23 has now been cancelled and this rejection can be withdrawn.

***E. The Rejection of Claims 18-21 and 23-27***

Claims 18-21 and 23-27 are rejected under 35 U.S.C. § 103(a) for obviousness over Devarajan 1 in view of Nelson. Claims 18-21 and 23-27 have been cancelled. This rejection can now be withdrawn.

**Rejection for Obviousness-type Double Patenting**

Claims 1, 4-13, 15-21, and 23-30 are provisionally rejected for obviousness-type double patenting over claims 1-14 of co-pending U.S. Serial No. 12/375,585 alone or in combination with Devarajan 1, Rose, and Clark, and over claims 1-15 and 16-17 of U.S. Serial No. 12/302,931 in view of one or more of Devarajan, Holvoet, Alocilja, Wu, Buechler, Fraser, Elneihoum, Forsblad, Rose, and Clark. Claims 16-21 and 23-29 have been cancelled. For the reason discussed above, Applicant believes that all of the present rejections against pending claims 1, 4-13, 15, and 30 have been addressed and should be withdrawn. As stated in M.P.E.P. § 804(I)(B)(1):

If a “provisional” nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer.

In this case, the present application is the earlier filed application of U.S. Serial No. 12/375,585 and U.S. Serial No. 12/302,931. Thus, the double patenting rejections against pending claims 1, 4-13, 15, and 30 should be withdrawn.

CONCLUSION

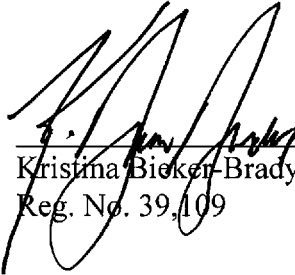
Applicant submits that present claims 1, 4-13, 15, and 30 are in condition for allowance, and such action is respectfully requested.

Submitted herewith is a Petition to extend the period of time for replying to the final Office Action by one (1) month, to and including April 8, 2011. Applicant authorizes the Office to deduct \$130.00 from Deposit Account No. 03-2095 for the fee required by 37 C.F.R. § 1.17(a). If there are any other charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date:

March 9, 2011

  
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Kristina Bieker-Brady, Ph.D.  
Reg. No. 39,109

Clark & Elbing LLP  
101 Federal Street  
Boston, MA 02110  
Telephone: 617-428-0200  
Facsimile: 617-428-7045