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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/708,462	02/18/2010	Steven Clyde Pettit	VBS0002-201-US	4486

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GLOBAL PATENT GROUP - VBS
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EXAMINER	
DRISCOLL, LORA E BARNHART	

ART UNIT	PAPER NUMBER
1653	

NOTIFICATION DATE	DELIVERY MODE
02/19/2013	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 12/708,462	Applicant(s) PETTIT ET AL.	
	Examiner Lora E. Barnhart Driscoll	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 December 2012.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 5) ☒ Claim(s) 1-33 is/are pending in the application.
- 5a) Of the above claim(s) 1-22 and 33 is/are withdrawn from consideration.
- 6) ☐ Claim(s) ____ is/are allowed.
- 7) ☒ Claim(s) 23-32 is/are rejected.
- 8) ☐ Claim(s) ____ is/are objected to.
- 9) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 11/18/10 (2), 2/21/11.
- 3) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____.
- 4) ☐ Other: ____.

DETAILED ACTION

Response to Amendments

Applicant's amendments filed 12/21/12 to claims 1 and 23 have been entered. Claim 33 has been added. Claims 1-33 remain pending.

The 12/21/12 claim amendments indicate that claim 1 is "presently amended," which is not a preferred status identifier. 37 C.F.R. § 1.121(c); see also M.P.E.P. § 714. Further, the amendments employ bold text, but there is no provision in 37 C.F.R. § 1.121(c) for using bold text in making amendments. Because the status of the claims under consideration is not in dispute, however, the examiner does not consider the reply sufficiently noncompliant to justify sending a notice. Future claim amendments that do not comply fully with 37 C.F.R. § 1.121(c) may necessitate the mailing of a notice of noncompliant amendment.

Election/Restrictions

Applicant's election of Group IV, claims 23-32, in the reply filed on 12/21/12 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant's election of the species "rice endosperm lumenal binding protein" and "transferrin" in the same reply is noted, but examination of this applicant has demonstrated that this requirement should be withdrawn.

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Claims 1-22 and 33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Examination on the merits commences on claims 23-32.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 23 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Luyten et al. (2003, U.S. Patent 6,617,161; reference A) taken in light of Berezenko et al. (2000, U.S. Patent 6,034,221; reference B).

Luyten teaches a complete culture medium for mammalian cells comprising 6.25 μ g transferrin and 1.25mg (1250 μ g) bovine serum albumin per mL, i.e. a ratio of 1

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to 200. (Column 3, lines 16-62; Table 1; see also Example 1, using the medium.)

Regarding the full scope of ratios in claim 23, Luyten teaches that the concentrations of the components can be adjusted to suit cell lines as necessary. (Column 3, lines 64-67.)

Luyten does not teach that the albumin is recombinant, produced in a plant, contains less than 1 EU endotoxin per mg, and is less than about 2% aggregates.

Berezenko teaches highly purified albumin that contains no detectable aggregates or endotoxin. (Column 1, lines 40-49; Examples 1 and 2.) Berezenko teaches that highly purified albumin is useful in supplementing media for higher eukaryotic cells. (Column 1, lines 21-23.) Berezenko exemplifies expressing albumin recombinantly. (Example 1 at column 5.) Berezenko teaches that highly purified albumin “is less likely to cause adverse side effects.” (Column 1, lines 56-57.)

A person of ordinary skill in the art would have had a reasonable expectation of success in substituting Berezenko’s highly purified albumin for the albumin in Luyten’s mammalian-cell-culture medium because Berezenko teaches that highly purified albumin is useful for eukaryotic cell culture. The skilled artisan would have been motivated to substitute Berezenko’s highly purified albumin for the albumin in Luyten’s mammalian-cell-culture medium because Berezenko’s albumin is highly pure and therefore causes few side effects. See also M.P.E.P. § 2144.04, part VII (“the mere purity of a product, by itself, does not render the product unobvious”).

The limitations “recombinant” and “produced in a plant” are product-by-process limitations. M.P.E.P. § 2113 reads, “Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps.”

“Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.” *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted).

The structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product. See, e.g., *In re Garnero*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979)

The use of 35 U.S.C. §§ 102 and 103 rejections for product-by-process claims has been approved by the courts. “[T]he lack of physical description in a product-by-process claim makes determination of the patentability of the claim more difficult, since in spite of the fact that the claim may recite only process limitations, it is the patentability of the product claimed and not of the recited process steps which must be established. We are therefore of the opinion that when the prior art discloses a product which reasonably appears to be either identical with or only slightly different than a product claimed in a product-by-process claim, a rejection based alternatively on either section 102 or section 103 of the statute is eminently fair and acceptable. As a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes

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put before it and then obtain prior art products and make physical comparisons therewith." *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972).

Once a product appearing to be substantially identical is found and an art rejection made, the burden shifts to the applicant to show an unobvious difference. In this case, Luyten and Berezenko both teach albumin in culture media, and Berezenko teaches producing albumin using recombinant-DNA technology in yeast. Applicant bears the burden of demonstrating that recombinant albumin made in yeast is materially different from recombinant albumin made in plants.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to substitute Berezenko's highly purified albumin for the albumin in Luyten's mammalian-cell-culture medium because Berezenko teaches that highly purified albumin is useful for eukaryotic cell culture and causes few side effects.

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Claims 23-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Deeter et al. (2007, WO 2007/002762 A2; foreign-patent reference #3 on 11/18/10 IDS) taken in view of Luyten et al. (2003, U.S. Patent 6,617,161), Potter et al. (1999, U.S. Patent 5,985,289; reference C), and Davies (1999, U.S. Patent 5,917,022; reference D).

Deeter teaches recombinant albumin made in rice, a plant. (Example 7 at paragraph 116.) Deeter's preparation method requires extracting rice flour in buffer and then clarifying the extract by filtration (paragraph 116); therefore, the albumin contains

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no aggregates that are larger than the filter Deeter employed (claim 23 places no limit on the size of the aggregates). Deeter also teaches recombinant lactoferrin made in rice, a plant. (Example 4 at paragraphs 106-110.) Deeter teaches culture-media formulations comprising 0.01-50 mg/mL lactoferrin (Example 5 at paragraph 111; Figure 20) and 100mg/L albumin (Example 8 at paragraph 118).

Deeter does not exemplify a single medium comprising both albumin and lactoferrin or suggest the ratios in claims 23 and 32. Deeter does not explicitly note that lactoferrin is related to transferrin. Deeter is silent as to the presence of endotoxin (claim 23) and rice heat-shock proteins (claims 24-28) in the albumin preparation.

Luyten teaches a complete culture medium for mammalian cells comprising 6.25 μ g (0.00625mg) transferrin and 1.25mg bovine serum albumin per mL, i.e. a ratio of 1 to 200. (Column 3, lines 16-62; Table 1; see also Example 1, using the medium.) Regarding the full scope of ratios in claim 23, Luyten teaches that the concentrations of the components can be adjusted to suit cell lines as necessary. (Column 3, lines 64-67.)

Potter teaches that transferrin and lactoferrin are both iron-chelating proteins. (Column 7, lines 15-16.) Lactoferrin is therefore a “transferrin-related protein.” Potter teaches that iron-chelating proteins can be employed in bacterial-culture media at varying concentrations to modulate iron content in the media as necessary for the cells. (Column 6, line 66, through column 7, line 21.)

Davies teaches that endotoxins are lipopolysaccharides that are found only in the cell wall of Gram-negative bacteria. (Column 1, lines 17-48.)

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A person of ordinary skill in the art would have had a reasonable expectation of success in combining Deeter's albumin and lactoferrin (which Potter teaches is a transferrin-related iron-chelating protein useful in in vitro culture) into a single medium because Deeter teaches that both of these components promote cell growth and Luyten teaches combining albumin with transferrin (another iron-chelating protein) in a single medium. Deeter, Luyter, and Potter all teach that albumin and transferrin/lactoferrin are useful culture-media additives that promote growth. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted). See M.P.E.P. § 2144.06.

The selection of the amount of albumin and lactoferrin to include when combining Deeter's media into one would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Luyten and Potter teach that the amounts of culture-media components may be modified as necessary for the cells being cultured and because Deeter exemplifies adding lactoferrin at various concentrations. Deeter exemplifies culture media comprising 0.01-50mg/mL lactoferrin (Example 5), and Luyten exemplifies a culture medium comprising 0.00625mg/mL transferrin (Table 1). Deeter exemplifies culture media comprising 0.1 mg/mL albumin (Example 8), and Luyten exemplifies a culture medium comprising 1.25mg/mL albumin. The references teach that iron-chelating proteins can promote cell growth across five

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orders of magnitude and that albumin promotes cell growth across two orders of magnitude, suggesting that the amount of each component added to the medium is not critical. The amount of each factor added to the medium is not clearly inventive, so the ratios of albumin and lactoferrin/transferrin would therefore also have constituted routine optimization at the time of the invention.

Deeter is silent as to the presence of endotoxin in the culture medium, but Davies teaches that endotoxin is a product of bacterial cells, not plant cells. A person of ordinary skill in the art would have had a reasonable expectation that Deeter's albumin and lactoferrin compositions, which were made by plants, contain no endotoxins.

Regarding claims 24-28, Deeter is silent as to the presence of heat-shock proteins, for example those recited in claims 26 and 27, in the albumin preparation. Deeter's method of preparing recombinant albumin from rice grain (Example 3 at paragraphs 103-105; Example 7 at 116-117), however, is identical to the one employed by applicants (Example 3 at page 100, line 1, through page 101, line 2; Example 5 at page 102, line 20, through page 103, line 9). M.P.E.P. § 2112 reads, "The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable." Something that is old does not become patentable upon the discovery of a new property, use, or application.

The Patent and Trademark Office is not equipped to conduct experimentation in order to determine whether or not the claimed recombinant albumin differs, and if so to what extent, from Deeter's recombinant albumin, which is made using a method identical to the one described in the instant specification. Deeter taken as a whole

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demonstrates a reasonable probability that Deeter's recombinant albumin is either identical or sufficiently similar to the claimed recombinant albumin that whatever differences exist are not patentably significant. Therefore, the burden of establishing novelty or unobviousness by objective evidence is shifted to applicants. The basis for claims 24-28's requirements for the presence of heat-shock proteins appears to be the experiment in Example 8 of the instant specification, which refer to peptide-mass fingerprinting of "three representative lots of recombinant albumin." (Page 115, line 26, through page 121, line 21.) Clear evidence that the Deeter's albumin does not possess a critical characteristic that is possessed by the claimed albumin (for example, a demonstration that Deeter's albumin does not contain the heat-shock proteins recited in claims 26 and 27) would advance prosecution and might permit allowance of claims to applicants' composition.

No claims are allowed. No claims are free of the art.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP 714.02 and 2163.06). In doing so, applicant is requested to refer to pages **and** line (or paragraph) numbers (if available) in the as-filed specification, **not** the published application. Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims and share an inventor or assignee with

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the instant application in order to assist the examiner with double patenting analysis in the application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart Driscoll, whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila G. Landau, can be reached on 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart Driscoll/
Primary Examiner, Art Unit 1653



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EXAMINER

DRISCOLL, LORA E BARNHART

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Office Action Summary	Application No. 12/708,462	Applicant(s) PETTIT ET AL.	
	Examiner Lora E. Barnhart Driscoll	Art Unit 1653	AIA (First Inventor to File) Status No

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Status

- 1) ☒ Responsive to communication(s) filed on 7/19.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 5) ☒ Claim(s) 23-34 is/are pending in the application.
5a) Of the above claim(s) 33 is/are withdrawn from consideration.
- 6) ☐ Claim(s) ____ is/are allowed.
- 7) ☒ Claim(s) 23-32 and 34 is/are rejected.
- 8) ☐ Claim(s) ____ is/are objected to.
- 9) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

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Application Papers

- 10) ☐ The specification is objected to by the Examiner.
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Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
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Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

- a) ☐ All b) ☐ Some c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

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Paper No(s)/Mail Date. ____. |
| 2) ☒ Information Disclosure Statement(s) (PTO/SB/08)
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DETAILED ACTION

This application is being examined under the pre-AIA first to invent provisions.

Response to Amendments

Applicant's amendments filed 7/19/13 to the claims have been entered. Claims 1-22 have been canceled. Claim 34 has been added. Claims 23-34 remain pending, of which claims 23-32 and 34 are being considered on their merits. Claim 33 remains withdrawn from consideration. References not included with this Office action can be found in a prior action. Any rejections of record not particularly addressed below are withdrawn in light of the claim amendments and applicant's comments.

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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Art Unit: 1653

consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claims 23, 31, and 34 are/remain rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Luyten et al. (2003, U.S. Patent 6,617,161) taken in light of Berezenko et al. (2000, U.S. Patent 6,034,221).

Luyten teaches a complete culture medium for mammalian cells comprising 6.25 μ g transferrin and 1.25mg (1250 μ g) bovine serum albumin per mL, i.e. a ratio of 1 to 200. (Column 3, lines 16-62; Table 1; see also Example 1, using the medium.) Regarding the full scope of ratios in claim 23, Luyten teaches that the concentrations of the components can be adjusted to suit cell lines as necessary. (Column 3, lines 64-67.) Regarding claim 34, Luyten teaches that the medium promotes cell growth. (Example 1 at column 5, lines 25-49.)

Luyten does not teach that the albumin is recombinant, produced in a plant, contains less than 1 EU endotoxin per mg, and is less than about 2% aggregates.

Berezenko teaches highly purified albumin that contains no detectable aggregates or endotoxin. (Column 1, lines 40-49; Examples 1 and 2.) Regarding claims 1 and 34, Berezenko teaches that highly purified albumin is useful in supplementing media for higher eukaryotic cells. (Column 1, lines 21-23.) Berezenko exemplifies expressing albumin recombinantly. (Example 1 at column 5.) Berezenko teaches that highly purified albumin "is less likely to cause adverse side effects." (Column 1, lines 56-57.)

A person of ordinary skill in the art would have had a reasonable expectation of success in substituting Berezenko's highly purified albumin for the albumin in Luyten's mammalian-cell-culture medium because Berezenko teaches that highly purified albumin is useful for eukaryotic cell culture. The skilled artisan would have been motivated to substitute Berezenko's highly purified albumin for the albumin in Luyten's mammalian-cell-culture medium because Berezenko's albumin is highly pure and therefore causes few side effects. See also M.P.E.P. § 2144.04, part VII ("the mere purity of a product, by itself, does not render the product unobvious").

The limitations "recombinant" and "produced in a plant" are product-by-process limitations. M.P.E.P. § 2113 reads, "Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps."

"Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted).

The structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive

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structural characteristics to the final product. See, e.g., *In re Garnero*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979)

The use of 35 U.S.C. §§ 102 and 103 rejections for product-by-process claims has been approved by the courts. “[T]he lack of physical description in a product-by-process claim makes determination of the patentability of the claim more difficult, since in spite of the fact that the claim may recite only process limitations, it is the patentability of the product claimed and not of the recited process steps which must be established. We are therefore of the opinion that when the prior art discloses a product which reasonably appears to be either identical with or only slightly different than a product claimed in a product-by-process claim, a rejection based alternatively on either section 102 or section 103 of the statute is eminently fair and acceptable. As a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith.” *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972).

Once a product appearing to be substantially identical is found and an art rejection made, the burden shifts to the applicant to show an unobvious difference. In this case, Luyten and Berezenko both teach albumin in culture media, and Berezenko teaches producing albumin using recombinant-DNA technology in yeast. Applicant bears the burden of demonstrating that recombinant albumin made in yeast is materially different from recombinant albumin made in plants, for example that yeast-produced albumin does not improve cell growth (claim 34).

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It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to substitute Berezenko's highly purified albumin for the albumin in Luyten's mammalian-cell-culture medium because Berezenko teaches that highly purified albumin is useful for eukaryotic cell culture and causes few side effects.

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Response to Arguments

Applicants allege that the claimed culture-media supplement "exhibits enhanced cell growth, viability, and productivity." (Reply at page 4.) Applicants refer in particular to Examples 7 and 17 in support of patentability. (Reply at pages 4-6.) These arguments have been fully considered, but they are not persuasive.

Burden of explaining proffered evidence

In submitting evidence asserted to establish unobvious results, there is a burden on an applicant to indicate how the examples asserted to represent the claimed invention are considered to relate to the examples intended to represent the prior art and, particularly, to indicate how those latter examples do represent the closest prior art. See *In re Borkowski*, 595 F.2d 713, 184 USPQ 29 (CCPA 1974); *In re Goodman*, 339 F.2d 228, 144 USPQ 30 (CCPA 1964). It is applicants, not the Office, who bear the burden of explaining data proffered as evidence of nonobviousness. M.P.E.P. § 716.02(b).

Applicants' reply refers to Example 17 and quotes a portion of that example in which applicants allege that "rice-derived recombinant human serum albumin produced

Observed Effect values much greater than the Predicted Effect.” (Reply at pages 4-5.) Applicants’ explanation ends there, so it is inadequate on its face because it provides no insight as to what “effect” was investigated or how it was “observed” or “predicted.” The examiner reviewed the specification for answers to these questions but found no satisfactory explanation. Example 11 indicates that “the Predicted Effect was calculated as the sum of the effect of the individual components” and refers to a Predicted Effect “where the predictive additive effect equals the sum of additive1 and additive2.” (Page 125, lines 5-6 and 12-14; see also page 137, lines 7-8.) These calculations do not clearly apply to Table E16,¹ however. For example, Table E16 indicates that the effect of rTF 1 mg/L alone is 0.10 and the effect of pHSA 5 g/L alone is 11.19, so the additive effect of those values is 11.29. Table E16, however, indicates that the “Predicted Effect” of rTF 1 mg/L + pHSA 5 g/L is 11.51. There is no clear explanation for this discrepancy; even if the 0.07 value for the “base medium” is added to the effects of the individual additives, the “Predicted Effect” (rTF + pHSA + base medium) is 11.36, not 11.51. These differences are pervasive in all three experiments depicted in Table E16.² It is wholly unclear how applicants arrived at their “Predicted Effect” values. Applicants have therefore not met their requirement to fully explain proffered data.

Scope of data vs. scope of claims

¹ The specification (page 138, line 4) and the reply (page 4) both refer to “Table E14,” but this is clearly a typographical error, as only Table E16 contains “the results of three independent experiments.” Table E14, depicted on page 134 of the specification, is an investigation of the effects on cell growth when selenium is included in the medium.

² For example, the Predicted Effect for the last line in Table E16 should be, at most, $(2.46 + 2.45 + 0.02) = 4.93$ (the total for rTF 3mg/L, rHSA 5g/L, and the base medium). Table E16 gives a Predicted Effect of 6.93.

Even if the “Predicted Effect” calculations in Table E16 were fully explained, the data would still be inadequate to overcome the rejection. Evidence of nonobviousness should also be reasonably commensurate in scope with the subject matter claimed and illustrate the claimed subject matter “as a class” relative to the prior art subject matter “as a class.” *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971); *In re Hostettler*, 429 F.2d 464, 166 USPQ 558 (CCPA 1970). To be given substantial weight in the determination of obviousness or nonobviousness, evidence of secondary considerations must be relevant to the subject matter as claimed, and therefore the examiner must determine whether there is a nexus between the merits of the claimed invention and the evidence of secondary considerations. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 305 n.42, 227 USPQ 657, 673-674 n. 42 (Fed. Cir. 1985), *cert. denied*, 475 U.S. 1017 (1986). The term “nexus” designates a factually and legally sufficient connection between the objective evidence of nonobviousness and the claimed invention so that the evidence is of probative value in the determination of nonobviousness. *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 7 USPQ2d 1222 (Fed. Cir.), *cert. denied*, 488 U.S. 956 (1988).

The data in Example 17 lacks the necessary nexus with the claimed subject matter. Example 17 is limited to experiments in which one type of cell (an unidentified mammalian hybridoma) is cultured in medium with recombinant transferrin (TF) and human serum albumin (HSA) either obtained from human serum or recombinantly produced in rice. (Page 136, line 21, through page 137, line 5.) The claims are not so

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limiting; they only require the presence of “a transferrin related protein” and “recombinant albumin . . . produced in a plant.”

Claim terms must be given their plain meaning unless they are otherwise defined in the specification. The best source for determining the meaning of a claim term is the specification - the greatest clarity is obtained when the specification serves as a glossary for the claim terms. The presumption that a term is given its ordinary and customary meaning may be rebutted by the applicant by clearly setting forth a different definition of the term in the specification. M.P.E.P. § 2111.01. If a claim term is given a particular limiting definition in the specification, that definition is controlling as to that term.

The term “transferrin related protein” is defined at page 61, lines 26-28, as referring to “transferrin family proteins including transferrin, lactoferrin, melanotransferrin, and ovotransferin [*sic*],” and “transferrin” is defined at page 62, line 18, through page 63, line 20, as “all naturally-occurring and synthetic forms of transferrin,” including recombinant transferrin, human transferrin, native transferrin, allelic variants of transferrin, mutants (deletions, additions, insertions, substitutions, and post-translational modifications), degradation products of transferrin, and homologs with as little as 30% identity to human, dog, cow, mouse, rat, chicken, or zebrafish transferrin. Lactoferrin, melanotransferrin, and ovotransferrin are likewise broadly defined. (Page 64, line 1, through page 65, line 22.) Claim 23, therefore, reads on all media that contain at least one of these transferrin-related proteins; by contrast, Example 17 employs “recombinant transferrin.” Even if claim 23 were limited to

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supplements comprising transferrin per se, Example 17 cannot demonstrate unexpected results across the entire scope of the claim. Example 7 suffers similar deficiencies and lacks the necessary nexus with claim 23 for the same reasons that Example 17 does.

Likewise, claim 23 only requires that the albumin be “recombinant” and “produced in a plant.” The term “albumin” is defined at page 56, line 22, through page 61, line 8, as “all naturally-occurring and synthetic forms of albumin,” including recombinant albumin, human albumin, allelic variants of albumin, mutants (deletions, additions, insertions, substitutions, and post-translational modifications), degradation products of albumin, and homologs with as little as 30% identity to human, chimp, dog, cow, mouse, rat, or chicken albumin. Claim 23, therefore, reads on all media that contain at least one of these albumins. By contrast, Example 17 is limited to investigations of two albumins: human serum albumin (HSA), obtained directly from human serum, and HSA produced recombinantly in one plant, transgenic rice (*Oryza sativa*). Even if claim 23 were limited to supplements comprising recombinant albumin per se “produced in a plant,” Example 17 cannot demonstrate unexpected results across the entire scope of the claim because it does not examine any albumin other than HSA and does not consider any plant other than transgenic *O. sativa*. Example 7 suffers similar deficiencies and lacks the necessary nexus with claim 23 for the same reasons that Example 17 does.

Significance of the results

It should also be established that the differences in the results are in fact unexpected and unobvious and of both statistical and practical significance. *In re Merck*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); *In re Longi*, 759 F. 2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Klosak*, 455 F2d 1077, 173 UAPQ 14 (CCPA 1972); *In re D'Ancicco*, 429 F.2d 1244, 169 USPQ 303 (CCPA 1971); *Ex parte Gelles*, 22 USPQ2d 1318 (BPAI 1992). Applicants' data fails to meet this standard.

Even if the "Predicted Effect" in Example 17 were properly described to permit consideration by the Office, the data in Example 17 does not demonstrate any result that appears truly unexpected. Example 17 demonstrates the effects of various additives on an undefined hybridoma's growth after 3 days in culture. (Page 137, line 5.) Predicted Effect might be, the data in Table E16 appears to demonstrate that human plasma-derived HSA has virtually the same effect on hybridoma cells as HSA produced recombinantly in rice. (Compare the value 7.79 for rTF 3mg/L + pHSA 5g/L with the value 8.33 for rTF 3mg/L + rHSA 5g/L.) Regardless of what applicants' Predicted Effect might be, the data in Table E16 does not appear to provide any unexpected results. Table E16 supports the Office's conclusion that the source of albumin is not material to patentability.

In addition, there is no clear practical or statistical significance to applicants' data. The specification provides no statistical analysis and does not even indicate how many replicates were employed in each experiment. It is also not clear that a modest increase in hybridoma viability after three days in culture is a practically significant outcome.

In short, applicants have failed to meet their burden in demonstrating that the invention as it is claimed yields unexpected results across its entire scope.

Regarding Berezenko, applicants allege that Figure 10 demonstrates that the host cell for the production of recombinant HSA is material to patentability. (Reply at page 5.) This data is inadequate for several reasons. First, the specification does not identify the tested albumins as “plant produced,” “yeast-derived,” or “human plasma derived” albumin. It refers to “CELLASTIM,” “CELLPRIME albumin,” and “plasma derived albumin (SERACARE).” Applicants’ reply alleges without basis that CELLASTIM is plant-produced HSA, CELLPRIME is yeast-produced HSA, and SERACARE is human-plasma-derived HSA. CELLASTIM appears to be a proprietary additive, and the examiner was unable to verify that it is plant-produced, much less identify the exact plant that is the source of the recombinant HSA. Likewise, Millipore (the manufacturer of CELLPRIME) does not indicate on its website that CELLPRIME is recombinant HSA produced in yeast, and the examiner was unable to verify applicants’ claim elsewhere online. The examiner was able to locate no information about the source of the HSA in SERACARE. Figure 10 represents the problems that arise when products are referred to by their trade names; the Office will not participate in the devaluation of trademarks. Extrinsic evidence demonstrating that applicants’ assertions about the source of HSA in CELLASTIM, CELLPRIME, and SERACARE are accurate would be probative.

In any event, even if applicants are correct about the contents of CELLASTIM, CELLPRIME, and SERACARE, Figure 10 contains no statistical analysis, its underlying experiments were carried out only twice, and it is unclear whether a three-fold increase

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in “specially conditioned AE1 hybridoma” numbers after 70 hours of culturing is practically significant. The data in Example 7 and Figure 10 are inadequate to demonstrate nonobviousness.

Applicants have not adequately explained how the specification’s data demonstrates nonobviousness, and the examiner’s independent consideration of applicants’ data has found no evidence of nonobviousness. The rejection stands.

Claims 23-32 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Deeter et al. (2007, WO 2007/002762 A2; foreign-patent reference #3 on 11/18/10 IDS) taken in view of Luyten et al. (2003, U.S. Patent 6,617,161), Potter et al. (1999, U.S. Patent 5,985,289), and Davies (1999, U.S. Patent 5,917,022).

Deeter teaches recombinant albumin made in rice, a plant. (Example 7 at paragraph 116.) Deeter’s preparation method requires extracting rice flour in buffer and then clarifying the extract by filtration (paragraph 116); therefore, the albumin contains no aggregates that are larger than the filter Deeter employed (claim 23 places no limit on the size of the aggregates). Deeter also teaches recombinant lactoferrin made in rice, a plant. (Example 4 at paragraphs 106-110.) Deeter teaches culture-media formulations comprising 0.01-50 mg/mL lactoferrin (Example 5 at paragraph 111; Figure 20) and 100mg/L albumin (Example 8 at paragraph 118).

Deeter does not exemplify a single medium comprising both albumin and lactoferrin or suggest the ratios in claims 23 and 32. Deeter does not explicitly note that

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lactoferrin is related to transferrin. Deeter is silent as to the presence of endotoxin (claim 23) and rice heat-shock proteins (claims 24-28) in the albumin preparation.

Luyten teaches a complete culture medium for mammalian cells comprising 6.25 μ g (0.00625mg) transferrin and 1.25mg bovine serum albumin per mL, i.e. a ratio of 1 to 200. (Column 3, lines 16-62; Table 1; see also Example 1, using the medium.) Regarding the full scope of ratios in claim 23, Luyten teaches that the concentrations of the components can be adjusted to suit cell lines as necessary. (Column 3, lines 64-67.)

Potter teaches that transferrin and lactoferrin are both iron-chelating proteins. (Column 7, lines 15-16.) Lactoferrin is therefore a "transferrin-related protein." Potter teaches that iron-chelating proteins can be employed in bacterial-culture media at varying concentrations to modulate iron content in the media as necessary for the cells. (Column 6, line 66, through column 7, line 21.)

Davies teaches that endotoxins are lipopolysaccharides that are found only in the cell wall of Gram-negative bacteria. (Column 1, lines 17-48.)

A person of ordinary skill in the art would have had a reasonable expectation of success in combining Deeter's albumin and lactoferrin (which Potter teaches is a transferrin-related iron-chelating protein useful in in vitro culture) into a single medium because Deeter teaches that both of these components promote cell growth and Luyten teaches combining albumin with transferrin (another iron-chelating protein) in a single medium. Deeter, Luyter, and Potter all teach that albumin and transferrin/lactoferrin are useful culture-media additives that promote growth. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same

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purpose, in order to form a third composition to be used for the very same purpose....

[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted). See M.P.E.P. § 2144.06.

The selection of the amount of albumin and lactoferrin to include when combining Deeter's media into one would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Luyten and Potter teach that the amounts of culture-media components may be modified as necessary for the cells being cultured and because Deeter exemplifies adding lactoferrin at various concentrations. Deeter exemplifies culture media comprising 0.01 -50mg/mL lactoferrin (Example 5), and Luyten exemplifies a culture medium comprising 0.00625mg/mL transferrin (Table 1). Deeter exemplifies culture media comprising 0.1 mg/mL albumin (Example 8), and Luyten exemplifies a culture medium comprising 1.25mg/mL albumin. The references teach that iron-chelating proteins can promote cell growth across five orders of magnitude and that albumin promotes cell growth across two orders of magnitude, suggesting that the amount of each component added to the medium is not critical. The amount of each factor added to the medium is not clearly inventive, so the ratios of albumin and lactoferrin/transferrin would therefore also have constituted routine optimization at the time of the invention.

Deeter is silent as to the presence of endotoxin in the culture medium, but Davies teaches that endotoxin is a product of bacterial cells, not plant cells. A person of

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ordinary skill in the art would have had a reasonable expectation that Deeter's albumin and lactoferrin compositions, which were made by plants, contain no endotoxins.

Regarding claims 24-28, Deeter is silent as to the presence of heat-shock proteins, for example those recited in claims 26 and 27, in the albumin preparation. Deeter's method of preparing recombinant albumin from rice grain (Example 3 at paragraphs 103-105; Example 7 at 116-117), however, is identical to the one employed by applicants (Example 3 at page 100, line 1, through page 101, line 2; Example 5 at page 102, line 20, through page 103, line 9). M.P.E.P. § 2112 reads, "The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable." Something that is old does not become patentable upon the discovery of a new property, use, or application.

The Patent and Trademark Office is not equipped to conduct experimentation in order to determine whether or not the claimed recombinant albumin differs, and if so to what extent, from Deeter's recombinant albumin, which is made using a method identical to the one described in the instant specification. Deeter taken as a whole demonstrates a reasonable probability that Deeter's recombinant albumin is either identical or sufficiently similar to the claimed recombinant albumin that whatever differences exist are not patentably significant. Therefore, the burden of establishing novelty or unobviousness by objective evidence is shifted to applicants. The basis for claims 24-28's requirements for the presence of heat-shock proteins appears to be the experiment in Example 8 of the instant specification, which refer to peptide-mass fingerprinting of "three representative lots of recombinant albumin." (Page 115, line 26,

through page 121, line 21.) Clear evidence that the Deeter's albumin does not possess a critical characteristic that is possessed by the claimed albumin (for example, a demonstration that Deeter's albumin does not contain the heat-shock proteins recited in claims 26 and 27) would advance prosecution and might permit allowance of claims to applicants' composition.

Response to Arguments

Applicants allege that their "new production process," B000C,³ yields recombinant HSA that "is functionally different from" HSA made using the "old production process," B000. (Reply at page 6.) Applicants point to the data in Tables E3 and E4 as evidence of patentability. (Reply at page 6.) Applicants allege that at the 5mg/mL level, the new process yields a product with "an average batch to batch 100 percent improvement in cell viability [and] an average 100-fold less endotoxin [and] detergent than in the old process." (Reply at page 6, quoting the specification at page 114, lines 17-20.) A closer review of the data in Tables E3 and E4, however, demonstrates that this improvement is only observed at the 5mg/mL and 10mg/mL data points. It is impossible to compare 1mg/mL of old HSA with 0.5mg/mL of new HSA. At the 2mg/mL data point, the standard deviation in the old preparation is such that the range of values overlaps with the values from the new preparation:

³ The specification refers to this production process as both B000C (page 111, line 16, e.g.) and B0000C (Table E4 at page 113). The examiner presumes that one of these is a typographical error. To avoid confusion, this Office action refers to the two processes as "new" (B000C/B0000C) and "old" (B000).

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	old 1mg/mL	new 0.5mg/mL	old 2mg/mL	new 2mg/mL	old 5mg/mL	new 5mg/mL	old 10mg/mL	new 10mg/mL
	15	13.1	7.9	15.7	4.1	13.4	0.9	11.2
	15.8	18.4	12.4	17.4	6.5	15.1	4.1	14.3
	16.3	15.4	11.1	17.2	5.2	14.1	2.9	12.1
	14	15.7	11.6	15.4	6.9	19.2	3.8	16.8
	14.9	12.5	2.3	15.8	0	15.1	0	14.6
	16.5	13.7	12.7	17.1	7.6	13.2	4	11
	15.3	15.5	11.4	17.5	7.1	17.2	2.7	14.7
	16.7	17.4	15.2	17.3	6.9	18.8	4.1	14.8
	17.5	17.9	19.1	16.3	15.4	16.6	8.5	13.7
	16.7	13.5	18.7	16	13.2	15.5	6.6	15.1
		11.1		14.4		12.5		11.7
average	15.9	14.9	12.2	16.4	7.3	15.5	3.8	13.6
std dev	1.1	2.4	4.9	1.0	4.3	2.2	2.5	1.9
+ std dev	16.9	17.3	17.2	17.4	11.6	17.7	6.2	15.5
- std dev	14.8	12.6	7.3	15.4	3.0	13.3	1.3	11.8

Despite the experimental results' clear indication that any effect of the new process is concentration-dependent, the claims are not limited to any particular concentration of HSA in the medium. The claims make various limitations about the ratio of albumin to transferrin, but none of them place a mg/mL limit on the albumin (or any other quantity). As was true regarding Example 17 and the rejection over Luyten in view of Berezenko, the results in Example 6 do not share a nexus with the scope of the claims.

Applicants rely on arguments traversing the above rejection to traverse this rejection (see reply at page 7, referring to Examples 7 and 17). Therefore, the response set forth above to arguments also applies to this rejection. In particular, applicants allege that "plant-produced albumin improves viability" compared to albumin from other sources. (Reply at page 7.) This argument fails to account for the scope of the claims

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because the experiments are limited to investigations of one albumin (HSA). The claims are not so limiting, only requiring an "albumin" (as broadly defined in the specification). Even if the specification did demonstrate some surprising effect on "viability," those observations would be limited to hybridomas, not to every cell (mammalian or otherwise) that can grow in the claimed albumin- and transferrin-containing medium.

No claims are allowed. No claims are free of the art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart Driscoll whose telephone number is (571)272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila G. Landau can be reached on 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart Driscoll/
Primary Examiner, Art Unit 1653



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/708,462	02/18/2010	Steven Clyde Pettit	VBS0002-201-US	4486

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GLOBAL PATENT GROUP - VBS
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EXAMINER

HOLLAND, PAUL J

ART UNIT	PAPER NUMBER
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1656

NOTIFICATION DATE	DELIVERY MODE
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06/03/2015

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

vtruman@globalpatentgroup.com
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Office Action Summary	Application No. 12/708,462	Applicant(s) PETTIT ET AL.	
	Examiner PAUL HOLLAND	Art Unit 1656	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02/06/2015.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

- 5) ☒ Claim(s) 23-34 is/are pending in the application.
5a) Of the above claim(s) 33 is/are withdrawn from consideration.
- 6) ☐ Claim(s) _____ is/are allowed.
- 7) ☒ Claim(s) 23-32 and 34 is/are rejected.
- 8) ☐ Claim(s) _____ is/are objected to.
- 9) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

- 10) ☒ The specification is objected to by the Examiner.
- 11) ☒ The drawing(s) filed on 06/28/2011 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

- a) ☐ All b) ☐ Some** c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) ☒ Notice of References Cited (PTO-892) | 3) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)
Paper No(s)/Mail Date _____ | 4) ☐ Other: _____ |

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DETAILED ACTION

Application Status

1. The present application is being examined under the pre-AIA first to invent provisions.
2. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.
3. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/18/2014 has been entered.
4. Applicant's supplemental amendment to the claims filed on 02/16/2015 in response to the Final Rejection mailed on 09/18/2013 is acknowledged. This listing of claims replaces all prior listings of claims in the application.
5. Claims 1-22 and 33-34 are indicated as being withdrawn; however, it is noted that claims 1-22 and 34 were listed as cancelled in the claim amendment filed on 03/18/2014 with the filing of the RCE. Accordingly, when filing the amendment on 02/16/2015, the text of claims 1-22 and 34 should not have been included. Applicant is directed to 37 CFR 1.121 regarding filing of amendments in the application. If applicant desired these claims to be entered, they should have been presented as new claims

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higher than claim 34. In the interest of compact prosecution, since original claim 34 was examined, it will be examined as part of this office action, but in any subsequent amendments should be renumbered.

6. Claims 23-34 are pending, of which claims 23-32 and 34 are examined on the merits.

7. Claim 33 stands withdrawn pursuant to 37 CFR 1.142(b).

8. Applicant's remarks filed on 03/18/2014 in response to the Final Rejection mailed on 09/18/2013 have been fully considered and are deemed persuasive to overcome at least one of the rejections and/or objections as previously applied.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in the prior Office Action.

Withdrawn Claim Rejections - 35 USC § 103

9. The rejection of claims 23, 31, and 34 under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Luyten et al. (2003, U.S. Patent 6,617,161; cited on PTO-892 mailed 02/19/2013) taken in light of Berezenko et al. (2000, U.S. Patent 6,034,221; cited on PTO-892 mailed 02/19/2013) is withdrawn in favor of the new rejections set forth below.

10. The rejection of claims 23-32 under 35 U.S.C. 103(a) as being unpatentable over Deeter et al. (2007, WO 2007/002762 A2; foreign-patent reference #3 on 11/18/10 IDS) taken in view of Luyten et al. (2003, U.S. Patent 6,617,161; cited on PTO-892 mailed 02/19/2013), Potter et al. (1999, U.S. Patent 5,985,289; cited on PTO-892 mailed 02/19/2013), and Davies (1999, U.S. Patent 5,917,022; cited on PTO-892 mailed 02/19/2013).

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Specification/Drawings

11. The specification and Drawings filed on 06/28/2011 are newly objected to for the following reasons:

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825; applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). To be in compliance, applicants should identify nucleotide sequences of at least 10 nucleotides and amino acid sequences of at least 4 amino acids in the specification by a proper sequence identifier, i.e., "SEQ ID NO:" (see MPEP 2422.01). If these sequences have not been listed in the computer readable form and paper copy of the sequence listing, applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d). In the instant case, Figures 1 and 5 of the specification and drawings contain sequences that are encompassed by the definition of amino acids and nucleotides without appropriate sequence identifiers.

Further, the disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the

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embedded hyperlink and/or other form of browser-executable code. See MPEP §

608.01. In the instant case, p. 2, lines 9 and 13 contain embedded hyperlinks.

New Claim Rejections - 35 USC § 112(b) or Second Paragraph

12. The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 23-32 and 34 are newly rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention. This new grounds of rejection is necessitated upon further consideration of the claims.

Regarding claims 23 (claim 34 dependent therefrom), 24 (claims 25-27 and 29-30 dependent therefrom), 28, and 31-32, the term "about" is a relative term which renders the claim indefinite. The term "about" is a term of degree and the examiner has reviewed the specification and while it is acknowledged that p. 23, lines 14-19 state "about" can mean within 1 or more than 1 standard deviation or "about" with respect to compositions can mean plus or minus a range of up to 20%, preferably up to 10%, more preferably up to 5%, these recitations are exemplary and non-limiting. It is suggested that applicant clarify the meaning of the claims.

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Further regarding claims 31-32, a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 31 recites the broad recitation 1 to 5000, and the claim also recites 1 to 50 which is the narrower statement of the range/limitation. Claim 32 recites the broad recitation 1 to 3, and the claim also recites 1 to 0.33, which is the narrower statement of the range/limitation.

New Claim Rejections - 35 USC § 112(d), or Fourth Paragraph

14. The following is a quotation of 35 U.S.C. 112(d):

(d) REFERENCE IN DEPENDENT FORMS.—Subject to subsection (e), a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), fourth paragraph:

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Subject to the [fifth paragraph of 35 U.S.C. 112 (pre-AIA)], a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

15. Claim 34 is newly rejected under 35 U.S.C. 112(d) or pre-AIA 35 U.S.C. 112, 4th paragraph, as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends. In the instant case, claim 34 fails to further limit claim 23, upon which it depends. Applicant may cancel the claim(s), amend the claim(s) to place the claim(s) in proper dependent form, rewrite the claim(s) in independent form, or present a sufficient showing that the dependent claim(s) complies with the statutory requirements.

New Claim Rejections - 35 USC § 101

16. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

17. Claims 23-32 and 34 are newly rejected under 35 U.S.C. 101 because the claimed invention is not directed to patent eligible subject matter. Based upon an analysis with respect to the claim as a whole, claim(s) 23-32 and 34 do not recite something significantly different than a judicial exception. The rationale for this determination is explained below: The claims encompass an albumin protein that is not markedly different in structure from that which is found in nature, such as rice albumin

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produced by *Oryza sativa* as disclosed by Mawal et al. (Bioscience Reports, 1987; examiner cited) or human serum albumin. Indeed, the specification defines "albumin" as encompassing naturally occurring albumin [see p. 56, bottom of the disclosure]. The recitation of "recombinant" or "produced in plants" is not sufficient to transform the supplement into something that is markedly different in structure because plants naturally undergo recombination, and furthermore, the albumin even if it is recombinantly produced in a heterologous host cell, would still be identical in structure to albumin that is found in nature. The dependent claims do not add anything significantly more to the naturally occurring albumin because claims 24-28 recite naturally occurring heat shock proteins that exist in rice. Also, dependent claims 29-32 recite transferrin and lactoferrin, which are not markedly different in structure than transferrin and lactoferrin that exist in human blood and would come in contact with human serum albumin. It is suggested that applicants amend the claims to demonstrate that the claimed proteins are markedly different in structure from those proteins which are naturally occurring.

New Claim Rejections - 35 USC § 102

18. The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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19. Claims 23-28 and 34 are newly rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Mawal et al. (*Bioscience Reports*, 1987; examiner cited) as evidenced by Davies (**US Patent Application** 5,917,022; cited on PTO-892 mailed 02/19/2013). This new grounds of rejection is necessitated upon further consideration of the prior art. See MPEP 2131.01.III regarding multiple reference 35 U.S.C. 102 rejections.

20. Claims 23-28 and 34 are drawn to a supplement or complete medium comprising: a recombinant albumin wherein said recombinant albumin is: i. produced in a plant; ii. has less than about 1 EU of endotoxin/mg of albumin; and iii. less than about 2% aggregated albumin; and wherein said supplement or complete medium improves growth of a cell in a cell culture medium comprising said supplement or complete medium.

21. With respect to claims 23-28 and 34, Mawal et al. teach a rice albumin from *Oryza sativa* that accounts for about 5% of the total seed proteins [see Abstract]. The rice albumin taught by Mawal et al. is interpreted as a supplement comprising recombinant albumin because plants undergo recombination as a natural process and a supplement can broadly and reasonably interpreted as any compound that can be added to anything. Indeed the entire rice seed or plant can be interpreted as a supplement. Although Mawal et al. does not explicitly teach that the supplement has less than about 1 EU endotoxin/mg of albumin, evidentiary reference Davies is cited in accordance with MPEP 2131.01.II to demonstrate that endotoxin is only found as lipopolysaccharides in the cell wall of Gram-negative bacteria [see Column 1, lines 17-48]. Since rice albumin comes from a rice plant and is not a bacteria, then the albumin

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taught by Mawal et al. would inherently lack any endotoxin. Although Mawal et al. does not explicitly teach that the supplement is less than about 2% aggregated albumin, and wherein said supplement or complete medium improves growth of a cell in cell culture medium comprising said supplement or complete medium; wherein said recombinant albumin comprises a heat shock protein selected from the group consisting of Rice HSP70, rice endosperm lumenal binding protein, Rice (gblACJ54890.11), EEC69073/OSI_37928, and AAB63469, it is the examiner's position that absent evidence otherwise that this activity and these proteins would be inherent to the rice seed albumin taught by Mawal et al. because the heat shock proteins are rice heat shock proteins and would therefore be present in *Oryza sativa*. Since the claims do not require that the supplement be actively improving the growth of a cell, and knowing that albumin is a supplement used in cell growth, it is the examiner's position that this would be an inherent feature of the rice seed albumin taught by Mawal et al.

MPEP 2112.I states "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999)". Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the rice albumin of the prior art does not possess the same material structural and functional characteristics of the claimed supplement comprising recombinant albumin). See *In re*

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Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594.

22. Claims 23-28 and 34 are newly rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Deeter et al. (**WO**2007/002762 A2; cited on IDS filed 11/18/10) as evidenced by Davies (**US Patent Application** 5,917,022; cited on PTO-892 mailed 02/19/2013). This new grounds of rejection is necessitated upon further consideration of the prior art. See MPEP 2131.01.III regarding multiple reference 35 U.S.C. 102 rejections.

23. With respect to claims 23-28 and 34, Deeter et al. teach components of cell culture medium produced from plant cells that improve the growth of a cell in the cell culture medium wherein the medium comprises human serum albumin produced in rice [see Abstract; paragraphs 0009 and 0116; Example 7]. Deeter et al. also teach clarifying the extracted rice human serum albumin by filtration and purification to approximately 98% (interpreted as no aggregation) [see paragraph 0116]. Although Deeter et al. does not explicitly teach that the supplement comprises less than about 1 EU of Endotoxin/mg of albumin, the reference of Davies is cited in accordance with MPEP 2131.01.II to demonstrate that endotoxin is only found as lipopolysaccharides in the cell wall of Gram-negative bacteria [see Column 1, lines 17-48]. Since the recombinant human serum albumin is produced in rice and is not a bacteria, then the human serum albumin taught by Deeter et al. would inherently lack any endotoxin.

Regarding claims 24-28, Deeter et al. is silent as to the presence of heat-shock proteins, for example those recited in claims 26 and 27, in the albumin preparation.

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Deeter's method of preparing recombinant albumin from rice grain [see Example 3 at paragraphs 103-105; Example 7 at 116-117), however, is identical to the one employed by applicants [see Example 3 at page 100, line 1, through page 101, line 2; Example 5 at page 102, line 20, through page 103, line 9]. It is the examiner's position that absent evidence otherwise, these proteins would be inherent to the recombinant human serum albumin produced by Deeter et al. MPEP 2112.I states "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999)". Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the rice albumin of the prior art does not possess the same material structural and functional characteristics of the claimed supplement comprising recombinant albumin). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594.

24. Claims 23 and 34 are newly rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Berezenko et al. (**US Patent** 6,034,221, 2000; cited on PTO-892 mailed 02/19/2013). This new grounds of rejection is necessitated upon further consideration of the prior art.

25. With respect to claims 23 and 34, Berezenko et al. teach highly purified albumin that contains no detectable aggregates or endotoxin [see Column 1, lines 40-49;

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Examples 1 and 2]. Berezenko et al. teaches that highly purified albumin is useful in supplementing media for higher eukaryotic cells [see Column 1, lines 21-23].

Berezenko et al. exemplifies expressing albumin recombinantly [Example 1 at column 5]. Berezenko et al. teach that highly purified albumin “is less likely to cause adverse side effects.” [see Column 1, lines 56-57]. Although Berezenko et al. does not teach that the albumin is produced in a plant, this recitation is a product-by-process claim.

MPEP 2113 states “[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.” *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)”. The Patent Office bears a lesser burden of proof in making out a case of *prima facie* obviousness for product-by-process claims because of their peculiar nature” than when a product is claimed in the conventional fashion. It is suggested that applicants demonstrate that the recited process steps of the product produce something that is markedly different and unexpected from what is obvious over the prior art of record.

New Claim Rejections - 35 USC § 103

26. The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been

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obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

27. Claims 29-32 are newly rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Deeter et al. (**WO**2007/002762 A2; cited on IDS filed 11/18/10) as evidenced by Davies (**US Patent Application** 5,917,022; cited on PTO-892 mailed 02/19/2013) in view of Luyten et al. (**US Patent** 6,617,161, 2003; cited on PTO-892 mailed 02/19/2013) and Potter et al. (**US Patent** 5,985,289, 1999; cited on PTO-892 mailed 02/19/2013). This new grounds of rejection is necessitated upon further review of the prior art.

28. The relevant teachings of Deeter et al. as applied to claims 23-28 and 34 are set forth above.

With respect to claims 29-32, Deeter et al. teach components of cell culture medium produced from plant cells that improve the growth of a cell in the cell culture medium wherein the medium comprises the addition of albumin, lactotransferrin, or transferrin recombinantly produced from plants [see Abstract; paragraphs 0006, 0009, 0061, 0071, and 0116; Example 7] at concentrations of 0.01-50 mg/mL of lactoferrin [see Example 5; paragraph 0111].

However, Deeter et al. does not teach the supplement of claim 29 comprising both albumin and lactoferrin; the supplement of claim 30 comprising both albumin and transferrin; the supplement of claim 31, wherein said ratio of said transferrin to said recombinant albumin is about 1 to 50, to about 1 to 5000; and the supplement of claim

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32, wherein said ratio of said lactoferrin to said recombinant albumin is about 1 to 3, to about 1 to 0.33.

Luyten et al. teach a complete culture medium for mammalian cells comprising 6.25 μ g (0.00625mg) transferrin and 1.25mg bovine serum albumin per mL, i.e. a ratio of 1 to 200 [see Column 3, lines 16-62; Table 1; see also Example 1, using the medium]. Regarding the full scope of ratios, Luyten et al. teach that the concentrations of the components can be adjusted to suit cell lines as necessary. [Column 3, lines 64-67].

Potter et al. teach that transferrin and lactoferrin are both iron-chelating proteins [see Column 7, lines 15-16]. Lactoferrin is therefore a “transferrin-related protein.” Potter et al. also teach that iron-chelating proteins can be employed in culture media at varying concentrations to modulate iron content in the media as necessary for the cells [see Column 6, line 66, through column 7, line 21].

At the time the invention was made it would have been obvious to one of ordinary skill in the art to combine the teachings of Deeter et al., Luyten et al., and Potter et al. according to the teachings of Luyten et al. and Potter et al. because Deeter et al. teach that albumin, transferrin, or lactoferrin produced in plants can be used to improve the growth of cells in a culture medium. Luyten et al. teach that the albumin and transferrin can be combined in a culture medium for cell growth. Potter et al. teach that lactotransferrin or transferrin can be employed in culture media at varying concentrations to modulate iron content in the media necessary for the cells. An ordinarily skilled artisan would have had a reasonable expectation of success, a reasonable level of predictability, and would have been motivated to combine the

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teachings of Deeter et al., Luyten et al., and Potter et al. because Luyten et al. acknowledges that albumin and transferrin can be combined in cell culture growth medium and Potter et al. acknowledges that both lactotransferrin and transferrin can be added to culture medium to modulate iron content. Therefore, the above invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Furthermore, MPEP 2144.06.I states “It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art.” *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be *prima facie* obvious.). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held *prima facie* obvious).” In the instant case, the improvement in cell growth by addition of plant derived albumin, lactotransferrin, or transferrin was known in the prior art as taught by Deeter et al. Therefore, it would have

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been obvious to one of ordinary skill in the art to combine these proteins as part of a culture medium to improve cell growth.

Although the combination of Deeter et al., Luyten et al., and Potter et al. do not explicitly teach the ratios of lactoferrin of about 1 to 3, to about 1 to 0.33, MPEP 2144.05.II.A states, "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[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." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)". In the instant case, it would be obvious to one of ordinary skill in the art to determine the appropriate workable ranges based on the teachings of Deeter et al., Luyten et al., and Potter et al.

Response to Remarks

29. Applicant's remarks filed on 03/18/2014 have been fully considered and are hereby rendered moot in view of the new rejections presented above.

In the interest of compact prosecution, the examiner has addressed applicant's remarks in regards to the product by process rejections over the claims.

Beginning on p. 5 of applicant's remarks, applicants in summary contend that the superior properties of plant-produced albumin arise, at least in part, from the contaminating heat shock proteins in the albumin, and therefore the production of albumin in plants is materially different than albumin produced by other means. Applicants present data, particularly Example 17 and Table E16 to demonstrate that the

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combination of rice produced albumin in combination with transferrin has a synergistic effect on the growth of cells as opposed to human serum albumin in combination with transferrin. Applicants contend that the claims does not include any other recombinant or non-recombinant albumin and one of ordinary skill in the art reading the claims in view of the specification would recognize that the recitation of "produced in a plant" as recited in the present claims provides significant and surprising beneficial effect on growth of a cell in a cell culture media supplement.

These arguments are found to be not persuasive because the scope of claims 23 and 34 only require an albumin protein having less than about 1 EU of endotoxin/mg of albumin; and less than about 2% aggregated albumin; and wherein said supplement or complete medium improves growth of a cell in cell culture medium comprising said supplement or complete medium. The claim does not require any other component structurally. It is clear from applicant's specification and remarks that the increased growth and beneficial properties of the supplement relates to the presence of contaminating heat shock proteins and not the albumin itself. Indeed, applicant's own disclosure at the top of p. 139 states "the ability of albumin to synergistically enhance the activity of transferrin and lactoferrin appears to dependent on the source of albumin, rather than being an inherent characteristic of the albumin itself". This statement suggests that there is no difference itself in the structure of albumin from the serum produced and rice produced albumin. Accordingly, given that the claim only requires the presence of albumin, the teachings of Berezenko et al. still reasonably read on the claims and the statements of MPEP 2113 applies. "[E]ven though product-by-process

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claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.” *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)”.

It is also noted that applicant’s alleged difference in structure of the plant produced albumin and the albumin produced in the prior art is not commensurate in scope with the claimed invention. It is apparent from applicant’s remarks and disclosure (see above) that the superiority of the product rests in the presence of contaminating heat shock proteins carried over from the production of the protein in rice and not the albumin itself. The claims read on any albumin produced by any plant, whereas the alleged difference in structure of the plant produced albumin occurs when it is produced in rice. There is no evidence of record that one of ordinary skill in the art would expect that production of any albumin in any plant would result in a superior product due to the carryover of contaminating heat shock proteins during the purification process.

Conclusions

30. Status of the claims:

Claims 23-34 are pending.

Claim 33 stands withdrawn pursuant to 37 CFR 1.142(b).

Claims 23-32 and 34 are rejected.

No claims are in condition for an allowance.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to PAUL HOLLAND whose telephone number is (571)270-3537. The examiner can normally be reached on m-f 8-5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/PAUL HOLLAND/
Examiner, Art Unit 1656

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EXAMINER

HOLLAND, PAUL J

ART UNIT	PAPER NUMBER
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1656

NOTIFICATION DATE	DELIVERY MODE
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12/21/2015

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 12/708,462	Applicant(s) PETTIT ET AL.	
	Examiner PAUL HOLLAND	Art Unit 1656	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12/03/2015.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

- 5) ☒ Claim(s) 23-32 is/are pending in the application.
5a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 6) ☐ Claim(s) _____ is/are allowed.
- 7) ☒ Claim(s) 23-32 is/are rejected.
- 8) ☐ Claim(s) _____ is/are objected to.
- 9) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

- 10) ☒ The specification is objected to by the Examiner.
- 11) ☒ The drawing(s) filed on 06/28/2011 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

- a) ☐ All b) ☐ Some** c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) ☐ Notice of References Cited (PTO-892) | 3) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)
Paper No(s)/Mail Date _____ | 4) ☐ Other: _____ |

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DETAILED ACTION

Application Status

1. The present application is being examined under the pre-AIA first to invent provisions.
2. Applicant's amendment to the claims filed on 12/03/2015 in response to the Non-Final Rejection mailed on 06/03/2015 is acknowledged. This listing of claims replaces all prior listings of claims in the application.
3. Claims 1-22 and 33-34 are cancelled.
4. Claims 23-32 are pending.
5. Applicant's remarks filed on 12/03/2015 in response to the Non-Final Rejection mailed on 06/03/2015 have been fully considered and are deemed persuasive to overcome at least one of the rejections and/or objections as previously applied.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in the prior Office Action.

Specification/Drawings

6. The objection to the specification for an embedded hyperlink is withdrawn in view of applicant's amendment to the specification to remove said hyperlink.
7. The objection to the specification and drawings filed on 06/28/2011 under 37 CFR 1.821(a)(1) and (a)(2) is maintained for the reasons of record and the reasons set forth below. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the

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requirements of 37 CFR 1.821 through 1.825; applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). To be in compliance, applicants should identify nucleotide sequences of at least 10 nucleotides and amino acid sequences of at least 4 amino acids in the specification by a proper sequence identifier, i.e., "SEQ ID NO:" (see MPEP 2422.01). If these sequences have not been listed in the computer readable form and paper copy of the sequence listing, applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d). In the instant case, Figures 1 and 5 of the specification and drawings contain sequences that are encompassed by the definition of amino acids and nucleotides without appropriate sequence identifiers.

RESPONSE TO REMARKS: The examiner has reviewed applicant's remarks filed on 12/03/2015 and found no traversal of the objection. Accordingly, the objection is maintained for the reasons of record.

Claim Objections

8. Claims 31-32 are newly objected to in the recitation of "1 to 50, to 1 to 5000" and "1 to 3, to 1 to 0.33", and in the interest of improving claim form, it is suggested that the comma be removed from the noted limitations. Appropriate correction is suggested.

Claim Rejections - 35 USC § 112(b) or Second Paragraph

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9. The rejection of claims 23-32 and 34 under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, for the relative term “about” is withdrawn in view of applicant’s amendment to the claims to remove said term.

10. The rejection of claims 31-32 under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, for reciting a broad range or limitation with a narrow range or limitation is withdrawn upon further consideration of the claims which appear to recite a range.

Claim Rejections - 35 USC § 112(d), or Fourth Paragraph

11. The rejection of claim 34 under 35 U.S.C. 112(d) or pre-AIA 35 U.S.C. 112, 4th paragraph, as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends is withdrawn in view of applicant’s amendment to the claims to cancel claim 34.

Claim Rejections - 35 USC § 101

12. The rejection of claim 34 under 35 U.S.C. 101 because the claimed invention is not directed to patent eligible subject matter is withdrawn in view of applicant’s amendment to the claims to cancel claim 34.

13. The rejection of claims 23-32 under 35 U.S.C. 101 because the claimed invention is not directed to patent eligible subject matter is maintained for the reasons of record and the reasons set forth below. Based upon an analysis with respect to the claim as a whole, claim(s) 23-32 and 34 do not recite something significantly different than a judicial exception. The rationale for this determination is explained below: The claims

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encompass an albumin protein that is not markedly different in structure from that which is found in nature, such as rice albumin produced by *Oryza sativa* as disclosed by Mawal et al. (Bioscience Reports, 1987; cited on PTO-892 mailed 06/03/2015) or human serum albumin. Indeed, the specification defines "albumin" as encompassing naturally occurring albumin [see p. 56, bottom of the disclosure]. The recitation of "recombinant" or "produced in plants" is not sufficient to transform the supplement into something that is markedly different in structure because plants naturally undergo recombination, and furthermore, the albumin even if it is recombinantly produced in a heterologous host cell, would still be identical in structure to albumin that is found in nature. The dependent claims do not add anything significantly more to the naturally occurring albumin because claims 24-28 recite naturally occurring heat shock proteins that exist in rice. Also, dependent claims 29-32 recite transferrin and lactoferrin, which are not markedly different in structure than transferrin and lactoferrin that exist in human blood and would come in contact with human serum albumin. It is suggested that applicants amend the claims to demonstrate that the claimed proteins are markedly different in structure from those proteins which are naturally occurring.

RESPONSE TO REMARKS: Beginning on p. 6 of applicant's remarks, applicants contend that the rice albumin disclosed by Mawal et al. and human albumin do not provide enough of a rationale to reject claims 23-32 because the recitation of the additional elements, recombinant albumin, produced in a plant, contains less than 1 EU endotoxin per mg, and is less than 2% aggregated albumin are additional elements that provides significantly more than the judicial exception.

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This argument is found to be not persuasive because given its broadest and reasonable interpretation, the claims read on a natural plant that produces albumin such as that disclosed by Mawal et al. Given its broadest and reasonable interpretation, a plant can be reasonably interpreted as a supplement. Furthermore, as stated in the rejection above, the recitation of "recombinant" or "produced in plants" is a product-by-process limitation and is not sufficient to transform the supplement into something that is markedly different in structure because even if the albumin is recombinantly produced in a heterologous host cell, it would still be identical in structure to albumin that is found in nature.

Claim Rejections - 35 USC § 102

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14. The rejection of claim 34 under pre-AIA 35 U.S.C. 102(b) as being anticipated by Mawal et al. (*Bioscience Reports*, 1987; cited on PTO-892 mailed 06/03/2015) as evidenced by Davies (**US Patent Application** 5,917,022; cited on PTO-892 mailed 02/19/2013) is withdrawn in view of applicant's amendment to the claims to cancel claim 34.

15. The rejection of claim 34 under pre-AIA 35 U.S.C. 102(b) as being anticipated by Deeter et al. (**WO**2007/002762 A2; cited on IDS filed 11/18/10) as evidenced by Davies (**US Patent Application** 5,917,022; cited on PTO-892 mailed 02/19/2013) is withdrawn in view of applicant's amendment to the claims to cancel claim 34.

16. The rejection of claim 34 under pre-AIA 35 U.S.C. 102(b) as being anticipated by Berezenko et al. (**US Patent** 6,034,221, 2000; cited on PTO-892 mailed 02/19/2013) is withdrawn in view of applicant's amendment to the claims to cancel claim 34.

17. The rejection of claims 23-28 under pre-AIA 35 U.S.C. 102(b) as being anticipated by Mawal et al. (*Bioscience Reports*, 1987; cited on PTO-892 mailed 06/03/2015) as evidenced by Davies (**US Patent Application** 5,917,022; cited on PTO-892 mailed 02/19/2013) is maintained for the reasons of record and the reasons set forth below.

18. As amended, claims 23-28 are drawn to a supplement or complete medium comprising: a recombinant albumin wherein said recombinant albumin is: i. produced in a plant; ii. has less than 1 EU of endotoxin/mg of albumin; and iii. less than 2% aggregated albumin; and wherein said supplement or complete medium improves

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growth of a cell in a cell culture medium comprising said supplement or complete medium.

19. With respect to claims 23-28, Mawal et al. teach a rice albumin from *Oryza sativa* that accounts for about 5% of the total seed proteins [see Abstract]. The rice albumin taught by Mawal et al. is interpreted as a supplement comprising recombinant albumin because plants undergo recombination as a natural process and a supplement can broadly and reasonably interpreted as any compound that can be added to anything. Indeed the entire rice seed or plant can be interpreted as a supplement. Although Mawal et al. does not explicitly teach that the supplement has less than about 1 EU endotoxin/mg of albumin, evidentiary reference Davies is cited in accordance with MPEP 2131.01.II to demonstrate that endotoxin is only found as lipopolysaccharides in the cell wall of Gram-negative bacteria [see Column 1, lines 17-48]. Since rice albumin comes from a rice plant and is not a bacteria, then the albumin taught by Mawal et al. would inherently lack any endotoxin. Although Mawal et al. does not explicitly teach that the supplement is less than about 2% aggregated albumin, and wherein said supplement or complete medium improves growth of a cell in cell culture medium comprising said supplement or complete medium; wherein said recombinant albumin comprises a heat shock protein selected from the group consisting of Rice HSP70, rice endosperm lumenal binding protein, Rice (gblACJ54890.11), EEC69073/OSI_37928, and AAB63469, it is the examiner's position that absent evidence otherwise that this activity and these proteins would be inherent to the rice seed albumin taught by Mawal et al. because the heat shock proteins are rice heat shock proteins and would therefore

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be present in *Oryza sativa*. Since the claims do not require that the supplement be actively improving the growth of a cell, and knowing that albumin is a supplement used in cell growth, it is the examiner's position that this would be an inherent feature of the rice seed albumin taught by Mawal et al.

MPEP 2112.I states “[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art’s functioning, does not render the old composition patentably new to the discoverer.” *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999)”. Since the Office does not have the facilities for examining and comparing applicants’ protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the rice albumin of the prior art does not possess the same material structural and functional characteristics of the claimed supplement comprising recombinant albumin). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594.

RESPONSE TO REMARKS: Beginning on p. 7 of applicant’s remarks, applicants contend that Mawal et al. does not anticipate a supplement of complete medium comprising recombinant albumin in a plant, but rather Mawal et al. provides a biochemical and immunological characterization of rice albumin. Further applicants contend that Mawal et al. does not disclose that the supplement has less than 1 EU endotoxin/mg albumin and less than 2% aggregated albumin.

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These arguments are found to be not persuasive because as stated in the rejection above and reiterated below, the rice albumin taught by Mawal et al. is interpreted as a supplement comprising recombinant albumin because plants undergo recombination as a natural process and a supplement can broadly and reasonably interpreted as any compound that can be added to anything. Indeed the entire rice seed or plant can be interpreted as a supplement. Although Mawal et al. does not explicitly teach that the supplement has less than about 1 EU endotoxin/mg of albumin, evidentiary reference Davies is cited in accordance with MPEP 2131.01.II to demonstrate that endotoxin is only found as lipopolysaccharides in the cell wall of Gram-negative bacteria [see Column 1, lines 17-48]. Since rice albumin comes from a rice plant and is not a bacteria, then the albumin taught by Mawal et al. would inherently lack any endotoxin. Although Mawal et al. does not explicitly teach that the supplement is less than about 2% aggregated albumin, and wherein said supplement or complete medium improves growth of a cell in cell culture medium comprising said supplement or complete medium; wherein said recombinant albumin comprises a heat shock protein selected from the group consisting of Rice HSP70, rice endosperm luminal binding protein, Rice (gblACJ54890.11), EEC69073/OSI_37928, and AAB63469, it is the examiner's position that absent evidence otherwise that this activity and these proteins would be inherent to the rice seed albumin taught by Mawal et al. because the heat shock proteins are rice heat shock proteins and would therefore be present in *Oryza sativa*. Since the claims do not require that the supplement be actively improving the growth of a cell, and knowing that albumin is a supplement used in cell growth, it is the

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examiner's position that this would be an inherent feature of the rice seed albumin taught by Mawal et al.

Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the rice albumin of the prior art does not possess the same material structural and functional characteristics of the claimed supplement comprising recombinant albumin). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594.

20. The rejection of claims 23-28 under pre-AIA 35 U.S.C. 102(b) as being anticipated by Deeter et al. (**WO2007/002762 A2**; cited on IDS filed 11/18/10) as evidenced by Davies (**US Patent Application** 5,917,022; cited on PTO-892 mailed 02/19/2013) is maintained for the reasons of record and the reasons set forth below.

21. With respect to claims 23-28, Deeter et al. teach components of cell culture medium produced from plant cells that improve the growth of a cell in the cell culture medium wherein the medium comprises human serum albumin produced in rice [see Abstract; paragraphs 0009 and 0116; Example 7]. Deeter et al. also teach clarifying the extracted rice human serum albumin by filtration and purification to approximately 98% (interpreted as no aggregation) [see paragraph 0116]. Although Deeter et al. does not explicitly teach that the supplement comprises less than about 1 EU of Endotoxin/mg of albumin, the reference of Davies is cited in accordance with MPEP 2131.01.II to demonstrate that endotoxin is only found as lipopolysaccharides in the cell wall of

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Gram-negative bacteria [see Column 1, lines 17-48]. Since the recombinant human serum albumin is produced in rice and is not a bacteria, then the human serum albumin taught by Deeter et al. would inherently lack any endotoxin.

Regarding claims 24-28, Deeter et al. is silent as to the presence of heat-shock proteins, for example those recited in claims 26 and 27, in the albumin preparation. Deeter's method of preparing recombinant albumin from rice grain [see Example 3 at paragraphs 103-105; Example 7 at 116-117), however, is identical to the one employed by applicants [see Example 3 at page 100, line 1, through page 101, line 2; Example 5 at page 102, line 20, through page 103, line 9]. It is the examiner's position that absent evidence otherwise, these proteins would be inherent to the recombinant human serum albumin produced by Deeter et al. MPEP 2112.I states "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999)". Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the rice albumin of the prior art does not possess the same material structural and functional characteristics of the claimed supplement comprising recombinant albumin). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594.

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RESPONSE TO REMARKS: Beginning on p. 7 of applicant's remarks, applicants contend that the present specification exemplifies differences between the B000 (old production process) and B000C (new production process), and that the new production process for the recombinant human serum albumin of the claimed invention is set forth. Applicants contend that the results of this process provide functional differences between recombinant albumin produced using the old process and the new process. Applicants further contend that the new process results in a combination of high albumin purity, relative lack of endotoxin and/or detergent, and co-purification of heat shock proteins that results in a product that out performs previous methods for preparing albumin. Accordingly, applicants contend that the recombinant albumin of Deeter et al. cannot be identical.

These arguments are found to be not persuasive because as stated in the rejection above, although Deeter et al. does not explicitly teach that the supplement comprises less than about 1 EU of Endotoxin/mg of albumin, the reference of Davies is cited in accordance with MPEP 2131.01.II to demonstrate that endotoxin is only found as lipopolysaccharides in the cell wall of Gram-negative bacteria [see Column 1, lines 17-48]. Since the recombinant human serum albumin is produced in rice and is not a bacteria, then the human serum albumin taught by Deeter et al. would inherently lack any endotoxin. As stated in the rejection and remarks for Mawal et al., since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the rice

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albumin of the prior art does not possess the same material structural and functional characteristics of the claimed supplement comprising recombinant albumin). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594.

22. The rejection of claim 23 under pre-AIA 35 U.S.C. 102(b) as being anticipated by Berezenko et al. (**US Patent** 6,034,221, 2000; cited on PTO-892 mailed 02/19/2013) is maintained for the reasons of record and the reasons set forth below.

23. With respect to claim 23, Berezenko et al. teach highly purified albumin that contains no detectable aggregates or endotoxin [see Column 1, lines 40-49; Examples 1 and 2]. Berezenko et al. teaches that highly purified albumin is useful in supplementing media for higher eukaryotic cells [see Column 1, lines 21-23].

Berezenko et al. exemplifies expressing albumin recombinantly [Example 1 at column 5]. Berezenko et al. teach that highly purified albumin “is less likely to cause adverse side effects.” [see Column 1, lines 56-57]. Although Berezenko et al. does not teach that the albumin is produced in a plant, this recitation is a product-by-process claim.

MPEP 2113 states “[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.” *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)”. The Patent Office bears a lesser burden of proof in making out a case of *prima*

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facie obviousness for product-by-process claims because of their peculiar nature” than when a product is claimed in the conventional fashion. It is suggested that applicants demonstrate that the recited process steps of the product produce something that is markedly different and unexpected from what is obvious over the prior art of record.

RESPONSE TO REMARKS: Beginning on p. 9 of applicant’s remarks, applicants contend that Berezenko et al. relates to the production of recombinant albumin in a microorganism using a cell culture system and not production of recombinant proteins in a multicellular organism such as a plant.

This argument is found to be not persuasive because as stated in the rejection above, although Berenzenko et al. does not teach that the albumin is produced in a plant, this recitation is a product-by-process claim. MPEP 2113 states “[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.” *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)”. The Patent Office bears a lesser burden of proof in making out a case of *prima facie* obviousness for product-by-process claims because of their peculiar nature” than when a product is claimed in the conventional fashion.

Claim Rejections - 35 USC § 103

24. The rejection of claims 29-32 under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Deeter et al. (**WO**2007/002762 A2; cited on IDS filed 11/18/10) as evidenced by Davies (**US Patent Application** 5,917,022; cited on PTO-892 mailed 02/19/2013) in view of Luyten et al. (**US Patent** 6,617,161, 2003; cited on PTO-892 mailed 02/19/2013) and Potter et al. (**US Patent** 5,985,289, 1999; cited on PTO-892 mailed 02/19/2013) is maintained for the reasons of record and the reasons set forth below.

25. The relevant teachings of Deeter et al. as applied to claims 23-28 are set forth above.

With respect to claims 29-32, Deeter et al. teach components of cell culture medium produced from plant cells that improve the growth of a cell in the cell culture medium wherein the medium comprises the addition of albumin, lactotransferrin, or transferrin recombinantly produced from plants [see Abstract; paragraphs 0006, 0009, 0061, 0071, and 0116; Example 7] at concentrations of 0.01-50 mg/mL of lactoferrin [see Example 5; paragraph 0111].

However, Deeter et al. does not teach the supplement of claim 29 comprising both albumin and lactoferrin; the supplement of claim 30 comprising both albumin and transferrin; the supplement of claim 31, wherein said ratio of said transferrin to said recombinant albumin is about 1 to 50, to about 1 to 5000; and the supplement of claim 32, wherein said ratio of said lactoferrin to said recombinant albumin is about 1 to 3, to about 1 to 0.33.

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Luyten et al. teach a complete culture medium for mammalian cells comprising 6.25 μ g (0.00625mg) transferrin and 1.25mg bovine serum albumin per mL, i.e. a ratio of 1 to 200 [see Column 3, lines 16-62; Table 1; see also Example 1, using the medium]. Regarding the full scope of ratios, Luyten et al. teach that the concentrations of the components can be adjusted to suit cell lines as necessary. [Column 3, lines 64-67].

Potter et al. teach that transferrin and lactoferrin are both iron-chelating proteins [see Column 7, lines 15-16]. Lactoferrin is therefore a “transferrin-related protein.” Potter et al. also teach that iron-chelating proteins can be employed in culture media at varying concentrations to modulate iron content in the media as necessary for the cells [see Column 6, line 66, through column 7, line 21].

At the time the invention was made it would have been obvious to one of ordinary skill in the art to combine the teachings of Deeter et al., Luyten et al., and Potter et al. according to the teachings of Luyten et al. and Potter et al. because Deeter et al. teach that albumin, transferrin, or lactoferrin produced in plants can be used to improve the growth of cells in a culture medium. Luyten et al. teach that the albumin and transferrin can be combined in a culture medium for cell growth. Potter et al. teach that lactotransferrin or transferrin can be employed in culture media at varying concentrations to modulate iron content in the media necessary for the cells. An ordinarily skilled artisan would have had a reasonable expectation of success, a reasonable level of predictability, and would have been motivated to combine the teachings of Deeter et al., Luyten et al., and Potter et al. because Luyten et al. acknowledges that albumin and transferrin can be combined in cell culture growth

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medium and Potter et al. acknowledges that both lactotransferrin and transferrin can be added to culture medium to modulate iron content. Therefore, the above invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Furthermore, MPEP 2144.06.I states “It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art.” *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be *prima facie* obvious.). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held *prima facie* obvious).” In the instant case, the improvement in cell growth by addition of plant derived albumin, lactotransferrin, or transferrin was known in the prior art as taught by Deeter et al. Therefore, it would have been obvious to one of ordinary skill in the art to combine these proteins as part of a culture medium to improve cell growth.

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Although the combination of Deeter et al., Luyten et al., and Potter et al. do not explicitly teach the ratios of lactoferrin of 1 to 3, to 1 to 0.33, MPEP 2144.05.II.A states, "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[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." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)". In the instant case, it would be obvious to one of ordinary skill in the art to determine the appropriate workable ranges based on the teachings of Deeter et al., Luyten et al., and Potter et al.

RESPONSE TO REMARKS: Beginning on p. 10 of applicant's remarks, applicants contend that none of the prior art references discloses or suggests a cell culture media supplement comprising a recombinant albumin produced in a plant as presently claimed. Applicants contend that it is easily recognized by a person of ordinary skill in the art that a plant-produced recombinant cell culture component is different from a cell culture component which is not produced in a plant. Applicants contend that the evidence of superior properties of plant-produced albumin are demonstrated by the fact that the presence of heat shock proteins in the albumin produced in the plants enhance the cell growth promoting properties of the albumin. Applicants contend that plant derived human serum albumin is able to act synergistically with plasma derived transferrin, which is not seen with plasma derived human serum albumin.

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These arguments are found to be not persuasive because the teachings of Luyten et al. and Potter et al. were not relied upon for production of albumin in plants. The production of albumin in plants has been addressed in the 102(b) rejection above based on the teachings of Deeter et al. The teachings of Luyten et al. and Potter et al. are disclosed to demonstrate that albumin and transferrin can be combined in cell culture growth medium and Potter et al. acknowledges that both lactotransferrin and transferrin can be added to culture medium to modulate iron content. As stated above, MPEP 2144.06.I states “It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art.” *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be *prima facie* obvious.). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held *prima facie* obvious).” In the instant case, the improvement in cell growth by addition of plant derived albumin, lactotransferrin, or transferrin was known in the prior art as taught by Deeter et al. Therefore, it would have

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been obvious to one of ordinary skill in the art to combine these proteins as part of a culture medium to improve cell growth.

Regarding the synergistic growth effect of plant derived human serum albumin with plasma derived transferrin, MPEP 2145.II states [m]ere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. *In re Wiseman*, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979) (Claims were directed to grooved carbon disc brakes wherein the grooves were provided to vent steam or vapor during a braking action. A prior art reference taught noncarbon disc brakes which were grooved for the purpose of cooling the faces of the braking members and eliminating dust. The court held the prior art references when combined would overcome the problems of dust and overheating solved by the prior art and would inherently overcome the steam or vapor cause of the problem relied upon for patentability by applicants. Granting a patent on the discovery of an unknown but inherent function (here venting steam or vapor) “would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art.” 596 F.2d at 1022, 201 USPQ at 661.); *In re Baxter Travenol Labs.*, 952 F.2d 388, 21 USPQ2d 1281 (Fed. Cir. 1991) (Appellant argued that the presence of DEHP as the plasticizer in a blood collection bag unexpectedly suppressed hemolysis and therefore rebutted any *prima facie* showing of obviousness, however the closest prior art utilizing a DEHP plasticized blood collection bag inherently achieved same result, although this fact was unknown in the prior art.).” In the instant case, the combination of albumin with transferrin as a cell

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culture supplement flows from the teachings of Deeter et al., Luyten et al. and Potter et al.

Even assuming *arguendo* that the synergistic effect of plant derived human serum albumin combined with plasma derived transferrin is an unexpected result, the claims do not require human serum albumin nor plasma derived transferrin. The claims are unlimited with respect to the type and source of albumin and transferrin. The argument of unexpected results must be commensurate in scope with the claimed invention. MPEP 716.02(d) states “whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the “objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support.” In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980)”.

Furthermore, as stated in the Non-Final Rejection mailed 06/03/2015, the scope of claims 23 and 34 only require an albumin protein having less than about 1 EU of endotoxin/mg of albumin; and less than about 2% aggregated albumin; and wherein said supplement or complete medium improves growth of a cell in cell culture medium comprising said supplement or complete medium. The claim does not require any other component structurally. It is clear from applicant's specification and remarks that the increased growth and beneficial properties of the supplement relates to the presence of contaminating heat shock proteins and not the albumin itself. Indeed, applicant's own disclosure at the top of p. 139 states “the ability of albumin to synergistically enhance

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the activity of transferrin and lactoferrin appears to dependent on the source of albumin, rather than being an inherent characteristic of the albumin itself". This statement suggests that there is no difference itself in the structure of albumin from the serum produced and rice produced albumin. It is also noted that applicant's alleged difference in structure of the plant produced albumin and the albumin produced in the prior art is not commensurate in scope with the claimed invention. It is apparent from applicant's remarks and disclosure (see above) that the superiority of the product rests in the presence of contaminating heat shock proteins carried over from the production of the protein in rice and not the albumin itself. The claims read on any albumin produced by any plant, whereas the alleged difference in structure of the plant produced albumin occurs when it is produced in rice. There is no evidence of record that one of ordinary skill in the art would expect that production of any albumin in any plant would result in a superior product due to the carryover of contaminating heat shock proteins during the purification process.

Conclusions

26. Status of the claims:

Claims 23-32 are pending.

Claims 23-32 are rejected.

No claims are in condition for an allowance.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to PAUL HOLLAND whose telephone number is (571)270-3537. The examiner can normally be reached on m-f 8-5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/PAUL HOLLAND/
Examiner, Art Unit 1656

/DAVID J. STEADMAN/
Primary Examiner, Art Unit 1656