UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TRANS OVA GENETICS, LC
Petitioner
v.
XY, LLC
Patent Owner

U.S. Patent No. 6,372,422
Issued: April 16, 2002
Filed: November 24, 1999
Inventors: George S. Seidel *et al.*

Title: Multiple Sexed Embryo Production System for Mammals

Case IPR2018-00249

PETITION FOR *INTER PARTES* REVIEW UNDER 35 U.S.C. §§ 311–319 AND 37 C.F.R. § 42

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I. INTRODUCTION

Trans Ova Genetics, L.C. ("Petitioner") requests IPR and cancellation of claims 1-4, 7-8, 10 and 13-14 of U.S. Patent No. 6,372,422 ("the '422 patent").

The challenged claims are drawn to a method of pharmaceutically inducing a non-human female mammal to produce multiple eggs and then, after the onset of estrus, inseminating the female mammal with sex-sorted sperm, thereby producing at least two "sexed embryos." This method, however, was not new. It had been known for years that sperm could be sex-sorted (*i.e.*, separated according to whether they carry an X or Y chromosome), that female mammals could be superovulated with pharmaceuticals, and that superovulated female mammals inseminated with sex-sorted sperm would produce sexed embryos and mammals.

Because the challenged claims recite nothing new, they should be canceled.

II. MANDATORY NOTICES

Pursuant to 37 C.F.R. § 42.8(b), Petitioner states as follows:

A. Real Parties In Interest. Trans Ova Genetics, L.C. and Intrexon Corporation are real parties in interest. No other parties exercised, or could have exercised, control over this Petition; no other parties funded or directed this Petition. *See* Office Patent Trial Practice Guide, 77 Fed. Reg. 48,759-60.

B. Related Matters. The '422 patent is the subject of pending litigation in the United States District Court for the District of Colorado (*XY, LLC et al. v.*

Trans Ova Genetics, *LC*, No. 1:17-cv-00944) ("Colorado litigation"), which was transferred from an earlier-filed case in the United States District Court for the Western District of Texas between the same parties (No. 6:16-cv-00447).

Petitioner also has filed petitions for IPR against two other patents owned by the Patent Owner, XY, LLC: U.S. Patent No. 7,723,116 (IPR2018-00247 and IPR2018-00248) and U.S. Patent No. 8,652,769 (IPR2018-00250).

C. Lead and Backup Counsel. Petitioner identifies the following:

Lead Counsel	Backup Counsel
David Kelly Registration No. 53,106 Hunton & Williams LLP 600 Peachtree St., N.E. Atlanta, GA 30308 Direct: 404.888.4280 Fax: 404.602.8671 dkelly@hunton.com	**Gene J. Yao** Registration No. 47,193 Hunton & Williams LLP 200 Park Ave., New York, NY 10166 Direct: 212.309.1030 Fax: 212.309.1877 gyao@hunton.com

D. Service Information. Please address all correspondence to both counsel shown above. Petitioner consents to electronic service by email to dkelly@hunton.com and gyao@hunton.com.

III. REQUIREMENTS FOR IPR REVIEW

Pursuant to 37 C.F.R. § 42.104, Petitioner states as follows:

A. Grounds for Standing. Petitioner certifies that the '422 patent is available for IPR and that Petitioner is not barred or estopped from requesting review on the grounds identified herein. The Director is authorized to charge the

fee specified by 37 C.F.R. § 42.15(a), and any other fees necessary, to Deposit Account No. 50-0206.

B. Identification of Challenge. Pursuant to 37 C.F.R. §§ 42.104(b) and 42.22(a)(1), Petitioner requests review and cancellation of claims 1-4, 7-8, 10, and 13-14 of the '422 patent pursuant to the following statement of the precise relief requested:

Ground	Claims	Basis	References
I	1-3, 7-8	§ 102	Hagele (Ex. 1005)
II	3, 7, and 8	§ 103	Hagele (Ex. 1005) and Seidel '91 (Ex. 1009)
III	4	§ 103	Hagele (Ex. 1005), Nowshari (Ex. 1016), and Donaldson (Ex. 1017)
IV	10, 13, and 14	§ 103	Hagele (Ex. 1005) and Spaulding (Ex. 1010)
V	10 and 14	§ 103	Hagele (Ex. 1005) Spaulding (Ex. 1010), and Rens (Ex. 1014)
VI	13 and 14	§ 103	Hagele (Ex. 1005), Johnson '92 (Ex. 1007), and Spaulding (Ex. 1010)

Pursuant to 37 C.F.R. § 42.22(a)(2), Petitioner sets forth a full statement of the reasons for the relief requested below in Section VIII. Petitioner's arguments are supported by a Declaration from David J. Miller, Ph.D. (Ex. 1003), Professor

of Animal Sciences at the University of Illinois, who has over 30 years of relevant experience, detailed in his C.V. (Ex. 1004.)

IV. LEVEL OF ORDINARY SKILL IN THE ART

The '422 patent is a based off an application that claims priority (through a chain of applications) to December 31, 1997. Without conceding that this priority claim is valid, Petitioner and its expert declarant, Dr. Miller, use December 31, 1997, as the relevant date for analysis of the level of skill and knowledge of a person of ordinary skill in the relevant art ("POSA").

The '422 patent relates to methods of inseminating a female mammal with sex-sorted sperm to produce two or more sexed embryos. A POSA for purposes of the '422 patent includes someone with at least a Bachelor of Science degree in the animal sciences, or closely related discipline, and at least 5 years' experience in one or more of the following areas: mammalian reproductive technologies, including egg fertilization techniques such as artificial insemination ("AI") and *in vitro* fertilization ("IVF"); study of the various factors that affect fertilization success; handling of mammalian sperm, including insemination and fertilization; embryo transfer; and/or the use of flow cytometric techniques to study and/or sort sperm. Ex. 1003 ¶ 18. Dr. Miller is qualified to opine from the perspective of a POSA. *Id*.

V. STATE OF THE RELEVANT ART

In summarizing the state of the art as of December 1997, Petitioner cites additional references beyond "prior art presented as the basis for obviousness," which "legitimately serve to document the knowledge that skilled artisans would bring to bear in reading the prior art identified as producing obviousness." *Ariosa Diagnostics v. Verinata Health*, *Inc.*, 805 F.3d 1359, 1365 (Fed. Cir. 2015).

A. Methods Of Pharmaceutically Inducing Superovulation In Non-Human Mammals And Inseminating Them Were Well-Known.

Methods of using ovulatory pharmaceuticals, such as follicle stimulating hormone ("FSH"), pregnant mare serum gonadotrophin (PMSG), and prostaglandin F-2-alpha ("PGF-2-alpha"), to induce superovulation in non-human mammals were well-known before December 1997. Ex. 1003 ¶¶ 27-28. In 1991, for example, Seidel authored an entire chapter on superovulatory treatments in non-human mammals, including cattle. Ex. 1009. Seidel details the common superovulation regimens, which include at least eight injections of FSH at half-day intervals with PGF-2-alpha given with the sixth or seventh FSH injection. *Id*., 28. Seidel '91 also describes inseminating female cows following superovulatory treatment (*id.*, 31-41), as well as collecting embryos from the inseminated cows (*id.*, 41-44).

Similarly, Johnson '97 disclosed superovulating female pigs (gilts) with an ovulatory pharmaceutical prior to insemination with sex-sorted sperm. Ex. 1018,

263-264. Additionally, Hagele disclosed superovulating cattle with ovulatory pharmaceuticals. In Hagele's method, normally cycling female cows were induced to superovulate on days nine to 12 of their estrous cycle with purified FSH ("FSH-P"), administered twice daily for 4.5 days. Ex. 1005, 295. Forty-eight hours after starting superovulation, Hagele administered Estrumate, a well-known PGF-2-alpha analogue. *Id*. Cows showing signs of estrus were then inseminated and produced multiple embryos. *Id*., 295, Table 1.

B. Methods Of Sex-Sorting Mammalian Sperm Were Well-Known.

Methods of sorting sperm based on the detectable difference in DNA content between X- and Y-bearing sperm were well known before December 1997. Ex. 1003 ¶ 29. Both Johnson '92 (Ex. 1007) and Spaulding (Ex. 1010) detail the systems and methods used to sort sperm cells using flow cytometry. *Id*.; *see also* Ex. 1007, 2:64-6:21; Ex. 1010, 7:42-10:8 (Example I).

C. Methods And Instruments For Sorting Mammalian Sperm At Greater Than 500 Sperm/Second Were Known.

By the early 1990s, enormous strides had been made in utilizing flow cytometry to sort mammalian sperm at increased sort speeds and yields. Ex. 1003 ¶ 30-31. Spaulding, for example, described in his 1991 patent improved methods and instruments for flow-sorting mammalian sperm. Ex. 1010, Abstract. Modifying a commercially-available Epics® Model 752 Flow Cytometer into a high-speed sperm-sorting instrument, Spaulding reported that the modified instrument was

"capable of analyzing and sorting [sperm] cells at rates up to 10,000 cells/second." *Id*., 8:7-8.

Similarly, Johnson '97 described modifying a commercially-available MoFlo® Flow Cytometer to sort at speeds 4-6 times faster than older unmodified systems, which could only sort up to about 111 sperm cells per second. Ex. 1018, 257, 260.

And Rens, which was filed in July 1997, described a high-speed sorter containing an elliptical-shaped nozzle that oriented sperm in a manner allowing for theoretical sample speeds "up to at least 15,000 sperm per second" and demonstrated sex-sorting speeds of about 2,000 sperm per second. Ex. 1014, 4:29-33; 7:46-57 (Example 7).

D. Methods Of Fertilizing Non-Human Mammals With Sex-Sorted Sperm To Produce Sexed Embryos Were Well-Known.

Methods of fertilizing non-human mammals, such as cattle and swine, with sex-sorted sperm also had been well-known before December 1997. Ex. 1003 ¶¶ 32-33. In Hagele, female cows were pharmaceutically induced to superovulate, and then inseminated with sex-sorted sperm, leading to the production of 57 sexed embryos. Ex. 1005, Abstract, 294-296, Table 1.

Similarly, Johnson '92 taught methods of fertilization in non-human mammals, such as deer and swine, using sex-sorted sperm to produce sexed embryos and sexed mammals. Ex. 1007, 7:1-33 (Examples 2-3).

Summarizing the state of the art in 1997, Johnson '97 noted that "[s]emen from most livestock species can now be successfully separated into predominantly X or Y sperm populations before their use [in AI or IVF] to produce sexed offspring." Ex. 1018, 255. Johnson '97 itself reported successfully fertilizing swine with sex-sorted sperm to produce sexed embryos and an 85-90% gender preselection success rate in the resulting litter of piglets. *Id*., 263-264.

VI. SUMMARY OF THE CLAIMED INVENTION

A. Brief Description Of The Challenged Claims

Claims 1-4, 7-8, 10, and 13-14 are being challenged. Claim 1, the only independent claim, recites:

1. A method of producing multiple, sexed embryos from a non-human female mammal comprising;
    a. creating superovulation in said female mammal to create at least two eggs comprising the step of using an ovulatory pharmaceutical to cause multiple eggs to be produced;
    b. determining a sex of a sperm cell of a male mammal;
    c. sorting according to said sex of said sperm cells;
    d. inserting at least a portion of said sorted sperm cells into a uterus of said female mammal after an onset of estrus; and
    e. fertilizing a plurality of said eggs to produce at least two sexed embryos of the desired sex from said female mammal.

Ex. 1001, cl. 1.

The remaining challenged claims all depend from claim 1. Claims 2-4, 7 and 8 further specify some aspect of the superovulation process, such as the timing and frequency of the ovulatory pharmaceutical usage, as well as additional pharmaceutical compounds to be included. Claim 2 recites that the superovulation is encouraged during the estrous cycle. Claim 3 recites that the ovulatory pharmaceutical is injected in half-day increments between days 2 and 18 of the estrous cycle; claim 4 depends from claim 3 and further requires at least seven injections, including injection of an estrus manipulation system on at least the sixth and seventh injections. Claim 7 recites injecting follicle stimulating hormone ("FSH") a plurality of times a day; claim 8 depends from claim 7, and further recites supplementing FSH with prostaglandin F-2-alpha ("PGF-2-alpha").

Claims 10, 13, and 14 further specify the steps involved in sorting the sperm. Claim 10 recites staining and then sorting the sperm cells at sorting rates of above 500, 1000, or 1200 sorts per second, and then concentrating the cells. Claim 13 recites producing a mammal of a desired sex by using the method of claim 1; claim 14 depends from claim 13, and further recites sorting at a rate of above 500, 1000, or 1200 sorts per second, and producing a sexed sperm cell specimen.

B. Summary Of The '422 Patent Specification

The '422 patent generally relates to methods of inseminating female mammals with sex-sorted sperm to produce multiple sexed embryos. Ex. 1001,

Abstract. The patent begins by disclosing methods of sorting sperm using high speed flow cytometers, such as the MoFlo®, which is discussed in various prior art documents. *Id*., 1:66-2:18; *see also id.*, 5:42-53 ("The isolation is preferably done through the use of flow cytometry. Flow cytometry in general is a technique which is well understood.").

One document that the '422 patent relies heavily is Johnson '92 (Ex. 1007), whose "technique of utilizing flow cytometry to separate X- and Y-chromosome bearing sperm has been so significant an advancement that it has for the first time made the commercial separation of such sperm feasible." *Id.*, 2:3-12; *see also id*., 3:23-28 (noting "the great advances by the Johnson patent and related technology"); 6:16-20 (stating that the cell sensing system is "discussed at length in the seminal work (no pun intended) by Larry Johnson, namely, U.S. Pat. No. 5,135,759."); *id.*, 6:55-67 (explaining that the cells are "stained according to the Johnson technique"); *id.*, 13:25-28 (same).[1]

[1] The '422 patent also discloses various minor modifications to the general method of sorting sperm, such as adding citrate or some other "chemically coordinated" substance to the sheath fluid (*id.*, 7:58-9:45), cushioning the impact of the sperm as they land in the collection elements (*id.*, 9:64-12:25), and/or providing low-dose samples of sorted sperm for artificial insemination (*id.*, 12:26-14:18). However, as not one of these modifications are recited in the challenged claims, none is relevant to this Petition.

The '422 patent also notes the importance of recent advances made to flow cytometers, including the MoFlo®, which have increased sorting speeds to 1,000 to 1,200 sorts per second, thus making commercial sorting of sperm feasible:

> One of the aspects of flow cytometry which is particularly important to its application for sperm sorting is the high speed operation of a flow cytometer. Advances have been particularly made by the flow cytometers available through Cytomation, Inc. under the MoFlo® trademark. These flow cytometers have increased sorting speeds extraordinarily and have thus made flow cytometry a technique which is likely to make feasible the commercial application of sperm sorting (among other commercial applications). They act to achieve high speed sorting, that is at a speed which is notably higher than those otherwise utilized. … In the application of a high speed cell sorter to the sorting of sperm cells, sorting at rates of greater than about 500 sorts per second is achieved. In fact, rates of ***sorting in the thousand and twelve hundred ranges have already been*** achieved through a high speed cell sorter.

Id., 7:1-11 (emphasis added).

After summarizing the general techniques of high-speed flow cytometry, the '422 patent discloses methods of inducing estrus and/or superovulation in cows with pharmaceutical drugs, such as PGF-2-alpha and FSH, respectively. *Id.*, 14:19-60. The patent notes that the use of PGF-2-alpha to synchronize estrus in cows was "well known in the art," and was "discussed in the article "Prostaglandin F2a-A

Fertility Drug in Dairy Cattle?", 18 *Theriogenology* 245 (1982)," authored by K.L. Macmillan (Ex. 1015). Ex. 1001, 14:19-27. The patent then provides an exemplary superovulation treatment in which 12 cows are treated with eight injections of FSH at half-day intervals and given PGF-2-alpha at the sixth and seventh FSH injection. *Id.*, 14:61-66. The patent reports that, after fertilization with sorted sex-sperm, 93% of recovered embryos were of the desired sex. *Id.*, 14:66-15:17.

The '422 patent closes with four Examples. *Id.*, 16:28-19:17. Female cows were induced into superovulation and then inseminated either with: (1) a high-dose sample of sex-sorted bull sperm (Example 1); (2) a normal dose of sex-sorted bull sperm (Example 3); (3) a low dose of frozen-thawed, unsorted sperm (Example 2); or (4) a low dose of sorted sperm (Example 4). *Id*. Pregnancies were confirmed and the sex of the fetuses determined about 1½ to 3 months after insemination. *Id*. The patent does not report whether any calves were born. Additionally, the inventors note that the results in Experiment 3 were "confounding" as "[f]ertility reduced drastically" depending on the type of bulls the semen was collected from and how the sperm were stored. *Id.*, 18:35-45. As such, the inventors concluded that "[f]urther studies are needed to determine whether variation observed in pregnancy rates was due to bull differences, insemination techniques, interval between sorting and insemination, or other factors." *Id.*, 18:45-48.

C. Summary Of The Relevant Prosecution History

The '422 patent issued from U.S. App. No. 09/448,643, filed November 24, 1999, as a continuation of U.S. App. No. 09/015,454, filed January 29, 1998, which in turn is a continuation-in-part of U.S. App. No. 09/001,394, filed December 31, 1997.

The prosecution of the '422 patent was short. Following the applicants' election of claims drawn to methods of producing multiple sexed embryos and an animal of a desired sex, the Office rejected the elected claims as obvious in view of multiple combinations of seven different prior art references. Ex. 1020, 5-12. The principal references cited in these rejections included Seidel '97 (Ex. 1011), Johnson '86 (Ex. 1012), and Cran (Ex. 1013). *Id*.

In the first rejection, the Office cited Seidel '97 as teaching essentially all the claimed steps except co-administration of FSH with PGF-2-alpha, which the Office asserted was taught in one or more secondary references. *Id.*, 5-7. In the second and third rejections, the Office cited Johnson '86 and Cran, respectively, as teaching essentially all of the claimed steps except superovulation with the recited combination of drugs prior to insemination, which the Office asserted was taught in one or more secondary references. *Id.*, 7-11. The Office also noted that, although the combined references did not teach the recited sort speed of greater than 500 sorts per second, such was taught in Rens (Ex. 1014). *Id.*, 12.

In December 2000, the applicants submitted a Rule 131 Declaration attempting to swear behind Seidel '97 and Cran. Ex. 1021. The applicants also traversed the rejections based on Johnson '86 as the principal reference by arguing that it merely suggests inseminating non-superovulated mammals but does not indicate whether the procedure taught therein would work on superovulated mammals. Ex. 1022, 8-9. "At best," the applicants argued, "the combined references … present only an 'obvious-to-try' situation." *Id.*, 10. Finally, the applicants distinguished Rens as only teaching a high sample rate, not a high sort rate. *Id.*, 12-15.

In March 2001, the Office withdrew its rejections based on Johnson '86 and Cran based on the applicants' arguments. Ex. 1023, 2. However, the Office rejected the applicants' reliance on the Rule 131 Declaration to overcome the rejections based on Seidel '97, asserting that the Declaration failed to establish conception and/or reduction to practice a method of inseminating a superovulated female mammal with sex-sorted sperm prior to Seidel. *Id.*, 5-6 (emphasis in original).

In response, the applicants submitted a Rule 132 Declaration from inventor George Seidel declaring that, as a co-author of Seidel '97, the reference could not be cited against his application because it was not a statutory bar. Ex. 1024; Ex. 1025, 3.

The Office subsequently allowed the claims on October 9, 2001, and the patent issued on April 16, 2002. Based on the priority application's filing date, and the fact that the patent received no PTA, it is set to expire on December 31, 2017.[2]

VII. CLAIM CONSTRUCTION

As the '422 patent expires on December 31, 2017—prior to institution of this IPR—the appropriate claim construction standard is similar to that of a district court. *See Samsung Elecs. Co. v. Koninklijke KPN N.V.*, IPR2016-00392, 2016 WL 5389053, Decision to Institute IPR (Patent Tr. & App. Bd., July 8, 2016), at 6 (citing *In re Rambus Inc.*, 694 F.3d 42, 46 (Fed. Cir. 2012)). In determining the meaning of the disputed claim limitation, the Board looks principally to the intrinsic evidence of record, examining the claim language itself, the written description, and the prosecution history. *Id*. There is a heavy presumption that a claim term carries its ordinary and customary meaning. *Id*. Moreover, only those terms that are in controversy need be construed, and only to the extent necessary to resolve the controversy. *Id*.

[2] To obviate a double-patenting rejection, the applicants filed a terminal disclaimer on September 21, 2001 over the parent application, U.S. Application No. 09/015,454 (now U.S. Patent No. 6,071,689), which had the same priority date. Ex. 1026. Thus, the terminal disclaimer had no effect on the term of the '422 patent.

Petitioner believes that all of the terms in the challenged claims should be accorded their ordinary and customary meaning. Those meanings, which are supported by the plain language of the claims and corroborated by the specification, are as follows:

A. "multiple, sexed embryos" (all challenged claims)

A POSA would understand this phrase to mean "two or more embryos created by fertilizing eggs with sex-sorted sperm, *i.e.*, sperm selected to be either X-bearing or Y-bearing." Ex. 1003 ¶ 53; *see also*, *e.g.*, Ex. 1001 at Abstract ("Improved insemination systems particularly adapted to use for sex-selected sperm sorting include systems which achieve superovulation and then multiple embryo production with sexed embryos."); *id.*, 5:42-45 ("As mentioned, the basic goal is that of separating the X-bearing sperm from the Y-bearing sperm. This is done in a manner which isolates the two types of sperm so that each can be separately packaged and dealt with."); *id.*, 15:49-51 ("Sexed semen would be useful for in vitro fertilization and to inseminate cows superovulated for embryo transfer.").

B. "determining a sex of a sperm cell" (all challenged claims)

A POSA would understand this phrase to mean "determining whether the sperm cell carries an X or Y chromosome." Ex. 1003 ¶ 54; *see also*, *e.g.*, Ex. 1001 at Abstract, 5:42-45, and 15:49-51.

C. "sorting according to said sex of said sperm cells" (all challenged claims)

A POSA would understand this phrase to mean "separating the sperm cells according to whether the cells carry an X or Y chromosome." Ex. 1003 ¶ 55; *see also*, *e.g.,* Ex. 1001 at Abstract, 5:42-45, and 15:49-51.

D. "fertilizing a plurality of said eggs to produce at least two sexed embryos of the desired sex from said female mammal" (all challenged claims)

A POSA would understand this phrase to mean "fertilizing multiple eggs with sperm selected to be either X-bearing or Y-bearing, thereby producing at least two embryos of the same sex (*i.e.*, male or female)." Ex. 1003 ¶ 56; *see also, e.g.*, Ex. 1001 at Abstract, 5:42-45, and 15:49-51.

E. "estrus manipulation system" (claims 4 and 8)

This term is not defined in the patent. However, the ordinary and customary meaning is simply "a system for manipulating estrus in a mammal." Ex. 1003 ¶ 57. The '422 patent claims and Examples make clear that such a system includes co-administering PGF-2-alpha along with FSH. *Id*.; *see also* Ex. 1001, claim 8 (reciting that "the step of incorporating an estrus manipulation system compris[es] the step of supplementing said dosage of follicle stimulating hormone with prostaglandin F-2-alpha."); *see also id.*, Examples 1, 2, and 4 (disclosing co-administration with PGF-2-alpha); *id.*, 14:61-66 ("By example, twelve Angus crossbred heifers were superovulated using standard procedures: 6, 6, 4, 4, 2, 2, 2,

and 2 mg FSH were injected intramuscularly at half-day intervals beginning between days 9 and 12 of the estrous cycle; 25 and 12.5 mg prostaglandin F-2 alpha were injected intramuscularly with the 6th and 7th FSH injections.").

F. "incorporating an estrus manipulation system at least on about the sixth and seventh injections" (claim 4)

The term "about" in the phrase "incorporating an estrus manipulation system at least ***on about*** the sixth and seventh injections" is not defined in the '422 patent. However, the use of the term "about" is generally understood to "avoid[] a strict numerical boundary" and must, rather, "be interpreted in its technologic and stylistic context." *Pall Corp. v. Micron Separations*, *Inc*., 66 F.3d 1211, 1217 (Fed. Cir. 1995). Here, a POSA reading the '422 patent would understand the phrase "on at least about" to provide some leeway with respect to the specific numbered injection on which the estrus manipulation system is co-administered. Ex. 1003 ¶ 58. A POSA would thus understand that the use of the phrase "on at least about" in the foregoing claim limitation to mean that the estrus manipulation system is incorporated as early as the fifth injection (if not earlier). *Id.*

G. "injecting a dosage of follicle stimulating hormone a plurality of times a day" (claim 7)

A POSA would understand this phrase to mean "injecting a follicle stimulating hormone two or more times a day." Ex. 1003 ¶ 59; *see also*, *e.g.*, Ex. 1001, claim 9 ("[W]herein injecting said dosage of follicle stimulating hormone a

plurality of times a day comprises injecting said follicle stimulating hormone in approximately ***half day increments***….") (emphasis added); *id.*, 14:61–64 ("By example, twelve Angus crossbred heifers were superovulated using ***standard procedures***: 6, 6, 4, 4, 2, 2, 2, and 2 mg FSH were injected intramuscularly at ***half-day intervals*** beginning between days 9 and 12 of the estrous cycle.") (emphasis added).

H. "prostaglandin F-2-alpha" (claim 8)

A POSA would understand the term "prostaglandin F-2-alpha" as encompassing PGF-2-alpha and its well-known analogues, such as Estrumate. Ex. 1003 ¶ 60. Specifically, the '422 patent expressly incorporates PGF-2-alpha analogues into its definition of the drug:

> In order to achieve conveniently timed artificial insemination, heifer or cow estrus may be synchronized using known techniques such as ***the utilization of prostaglandin F2α according to techniques well known in the art***. This latter substance may be particularly valuable in that it has been reported to potentially achieve enhanced fertility in heifers ***as discussed in*** the article "Prostoglandin F2α—A Fertility Drug in Dairy Cattle?", 18 Theriogenology 245 (1982) ***hereby incorporated by reference.***

Ex. 1001, 14:19-27 (emphases added).

The article incorporated by reference, Macmillan (Ex. 1015), discloses the use of prostaglandin analogues to synchronize estrus in cows. Ex. 1015, 247 ("A

prostaglandin analogue (Estrumate, ICI, UK) was used in trials 1 to 8. Each cow was injected once or twice with 2 ml containing 0.5 mg of cloprostenol (Table I)."); *id.* at 245 ("Reviews have highlighted the potential for using prostaglandin F2α (PGF) or its analogues to achieve acceptable levels of estrus synchrony in cattle and to thus dispense with the need for detection of estrus (1,2)."); *see also* Ex. 1003 ¶ 61.

As Macmillan is touted by the '422 patent as exemplary of well-known techniques for utilizing "prostaglandin F2α," and as Macmillan specifically discloses Estrumate—a PGF-2-alpha ***analogue***—a POSA would understand that the term "prostaglandin F-2-alpha" as utilized by the '422 patent inventors necessarily encompasses PGF-2-alpha analogues. Ex. 1003 ¶ 62.

I. "sexed cell sperm specimen" (claim 14)

A POSA would understand this term to mean "a sample of sperm that has been selected to be either X-bearing or Y-bearing and extended to the desired dosage level." Ex. 1003 ¶ 63. This construction is consistent with the specification, which only mentions the term "specimen" twice, each time in the context of a sorted sperm sample having a sufficient dosage for insemination purposes. *See* Ex. 1001, 14:11-18 (explaining that after the "sample" has been sorted, extended, and then diluted "to the desired dosage level," [t]he sperm cell specimen may then be placed in a straw for use in artificial insemination and may be transported to the

cows or heifers to be inseminated"); *id.*, 16:7-11 ("As a result of the insemination, it is of course desired that an animal of the desired sex be produced. This animal may be produced according to the systems discussed earlier through the use of the sexed sperm specimen.").

VIII. DETAILED DISCUSSION OF HOW EACH GROUND RAISES A REASONABLE LIKELIHOOD OF UNPATENTABILITY

Pursuant to Rule 42.104(b), this section demonstrates that the challenged claims are unpatentable. Ex. 1003 ¶¶ 65-136.

A. Each of the Relied-Upon References is Authentic, Admissible Prior Art to the '422 Patent

Petitioner relies on the following references:

1. Hagele (Ex. 1005) – Hagele was not cited during the prosecution of the '422 patent. Hagele published in a 1984 volume of the journal *Canadian Journal of Comparative Medicine*, and is thus prior art to the '422 patent claims under pre-AIA 35 U.S.C. § 102(b). As detailed in the accompanying declaration of Jonathan H. Hartnett, a librarian with the law firm of Hunton & Williams LLP, Exhibit 1005 is an authentic, admissible copy of the Hagele reference under the Federal Rules of Evidence. Ex. 1002.

2. Seidel '91 (Ex. 1009) – Seidel '91 was not cited during the prosecution of the '422 patent. Seidel '91 published in a Food and Agriculture Organization (FAO) Animal Production and Health Paper in 1991, and is thus prior

art to the '422 patent claims under pre-AIA 35 U.S.C. § 102(b). As detailed in Mr. Hartnett's Declaration, Exhibit 1009 is an authentic, admissible copy of the Seidel '91 reference under the Federal Rules of Evidence. Ex. 1002.

3. Nowshari (Ex. 1016) – Nowshari published in a 1995 volume of the journal *Theriogenology*, and is thus prior art to the '422 patent under pre-AIA 35 U.S.C. § 102(b). As detailed in Mr. Hartnett's Declaration, Exhibit 1016 is an authentic, admissible copy of the Nowshari reference under the Federal Rules of Evidence. Ex. 1002.

4. Donaldson (Ex. 1017) – Donaldson published in a 1985 volume of the journal *The Veterinary Record*, and is thus prior art to the '422 patent under pre-AIA 35 U.S.C. § 102(b). As detailed in Mr. Hartnett's Declaration, Exhibit 1017 is an authentic, admissible copy of the Donaldson reference under the Federal Rules of Evidence. Ex. 1002.

5. Spaulding (Ex. 1010) – Spaulding is a United States patent that issued in 1991, and is thus prior art to the '422 patent claims under pre-AIA 35 U.S.C. § 102(b). Exhibit 1010 is an authentic, admissible copy of the Spaulding reference under the Federal Rules of Evidence.

6. Johnson '92 (Ex. 1007) – Johnson '92 is a United States patent that issued in 1992, and is thus prior art to the '422 patent claims under pre-AIA 35 U.S.C. § 102(b). Johnson '92 was successfully applied as prior art against U.S.

Patent No. 7,195,920, which shares common inventorship and priority with the '422 patent, in *ABS Global, Inc. v. XY, LLC*, IPR 2014-01161, 2016 WL 125494, Final Written Decision (Paper 26) (Patent Tr. & App. Bd., Jan. 11, 2016). Ex. 1019. Exhibit 1007 is an authentic, admissible copy of the Johnson '92 reference under the Federal Rules of Evidence.

7. Rens (Ex. 1014) – Rens is a United States patent that was filed on July 24, 1997, and issued on November 16, 1999, and is thus prior art to the '422 patent claims under pre-AIA 35 U.S.C. § 102(e). Rens was successfully applied as prior art against U.S. Patent No. 7,195,920, which shares common inventorship and priority with the '422 patent, in IPR 2014-01161 (Paper 26). Ex. 1019. Exhibit 1014 is an authentic, admissible copy of the Rens reference under the Federal Rules of Evidence.

Each of Exhibits 1005 (Hagele), 1009 (Seidel '92), 1016 (Nowshari), 1017 (Donaldson), 1010 (Spaulding), and 1007 (Johnson '92) is over 20 years old, and each was prepared before January 1, 1998; as such, each qualifies as an ancient document under Fed. R. Evid. 803(16), both before and after the pending amendment to the Rule. Moreover, all of these Exhibits, as well as Exhibit 1014 (Rens), meet the residual exception to hearsay under Fed. R. Evid. 807 as each: (i) equivalent circumstantial guarantees of trustworthiness; (ii) is offered as evidence of a material fact; (iii) is more probative on the point for which it is

offered than any other evidence that Petitioner can obtain through reasonable efforts; and as (iv) admitting the Exhibit will best serve the purposes of the Federal Rules of Evidence and the interests of justice.

Additionally, Exhibits 1010 (Spaulding), 1007 (Johnson '92), and 1014 (Rens) are issued United States Patents, and thus each meets the public records exception to hearsay under Fed. R. Evid. 803(8).

B. Ground 1: Claims 1-3 and 7-8 Are Anticipated By Hagele.

As detailed below, Hagele discloses all the elements of claims 1-3 and 7-8.[3] Hagele reports using sex-sorted bull sperm to preselect the gender of the calves resulting from fertilizing superovulating cows. More specifically, Hagele induced over two dozen normally cycling cows into superovulating on days nine to 12 of their estrous cycle with a purified form of follicle stimulating hormone, FSH-P. The total dose for FSH-P was 45 mg, administered in 5-mg doses twice daily for 4.5 days. Two days after the FSH-P administrations began, Hagele administered

[3] As discussed herein, Hagele discloses each limitation of claims 1-3, 7, and 8, and thus anticipates these claims. However, should the PTAB deem that Hagele fails to expressly or inherently disclose each limitation of these claims, then it should hold that Hagele renders these claims obvious. Indeed, any differences between claims 1-3 and 7-8 and Hagele are such that the claims as a whole would have been obvious to a POSA at the time the invention was made. Ex. 1003, pg. 28, fn. 2.

625 μg of Estrumate, a PGF-2-alpha analogue. Cows showing signs of estrus were then inseminated with sex-sorted sperm, resulting in multiple sexed embryos.

Claim 1 (preamble): A method of producing multiple, sexed embryos from a non-human female mammal comprising:

To the extent this preamble is limiting, it is taught by Hagele. Ex. 1003 ¶¶ 65-67. Specifically, Hagele studied the effect of sex-sorting bull semen on the sex ratio of resulting embryos. Ex. 1005, Abstract. Hagele began by noting the advantages to being able to preselect the gender of food-producing animals:

> There would be obvious advantages to altering the sex ratio in food producing animals, whereas, in man, the ability to preselect sex could be a means of preventing sex-linked diseases or of controlling the size of the population.

Id., 294.

Hagele thus sought to study embryos produced using sex-sorted bull semen. *Id*., Abstract, 295 ("This paper presents results of sexing, by chromosomal analysis, day 12 to day 15 embryos collected from 14 superovulated donors inseminated with semen which had been separated into X and Y chromosome-bearing spermatozoa fractions by a thermal convection counter-streaming sedimentation and forced convection galvanization process (16).").

To that end, Hagele took 25 normally cycling cows, 20 to 60 months of age, and induced them to superovulate on days nine to 12 of their estrous cycle with

either FSH-P or PMSG. *Id.*, 295. Forty-eight hours after the FSH-P administrations began, Hagele administered cloprostenol (Estrumate), a well-known PGF-2-alpha analogue. *Id.*; *see also* Ex. 1003 ¶ 66.

Table 1 presents the data on the embryos "obtained from 14 superovulated donors inseminated with semen separated into X and Y-chromosome-bearing spermatozoa fractions of separated semen." Ex. 1005, 295 (Table). As shown in the table, multiple sexed embryos were obtained. *Id.*; *see also id.*, Abstract ("Fifty-seven embryos were sexed; 20 from Y chromosome-bearing and 37 from X chromosome-bearing fractions of semen.").

Claim 1(a): creating superovulation in said female mammal to create at least two eggs comprising the step of using an ovulatory pharmaceutical to cause multiple eggs to be produced;

See analysis of Claim 1 (preamble). Additionally, according to Hagele:

> Twenty-five, normally cycling, cross-bred beef cows, 20 to 60 months of age, were ***superovulated on days 9 to 12 of their estrous cycle*** with either follicle stimulating hormone (***FSH-P***) (Burns-Biotec Laboratories, Nebraska), ***or*** pregnant mare serum gonadotrophin (***PMSG***) (Elea Laboratories, Saladillo, Buenos Aires, Argentina).

Ex. 1005, 295 (emphases added).

Claim 1(b): determining a sex of a sperm cell of a male mammal;

As noted in Section VII above, a POSA would understand the phrase "determining a sex of a sperm cell" to mean "determining whether the sperm cell

carries an X or Y chromosome." Ex. 1003 ¶ 54. Hagele specifically discloses determining the sex (X or Y) of the sperm collected from bulls:

> Semen from six beef and six dairy bulls was collected…. A sedimentation galvanization cell (17) was filled with extended ejaculate and allowed to run for one to two hours at 6°C. ***Spermatozoa from ejaculates which showed spermatozoa migration into both anodic (Y chromosome-bearing) and cathodic (X chromosome bearing) chambers of the sedimentation galvanization cell were collected***, centrifuged and washed free of the particle-free extender by centrifugation and drawing off the supernatant fluid…. Semen straws were loaded, labelled, color coded for male or female fractions and frozen in liquid nitrogen vapor.

Ex. 1005, 295 (emphasis added); *see also id.*, Abstract ("Seventy-six, day 12 to day 15 bovine embryos, collected from 14 donors which had been inseminated with either X or Y chromosome-bearing spermatozoa fractions of semen separated by a thermal convection counterstreaming sedimentation and forced convection galvanization process, were processed for sexing by chromosomal analysis.").

Additionally, Hagele evaluated the efficacy of its sex-sorting process and determined the percentage of X- and Y-bearing sperm cells in each fraction:

> *In vitro* evaluation of the separation process was attempted on X and Y chromosome-bearing spermatozoa fractions from five of the 12 bulls by staining with quinacrine mustard (17) and determining the

> percentage of spermatozoa with (positive - male) and without (negative - female) anterior fluorescing bodies (B-bodies).

Id., 295.

Hagele concluded that separation indeed occurred, with samples taken from three bulls (Bulls A, B, and C) containing 90%, 85%, and 85% Y-bearing sperm, and 70%, 70%, and 75% X-bearing sperm, respectively. *Id.*, 296. Further, Hagele Table 1 shows that female cows were inseminated with fractions that were predominantly X- or Y-bearing. *Id.* (Table 1); *see also* Ex. 1003 ¶ 70-71.

Claim 1(c): sorting according to said sex of said sperm cells;

As noted in Section VII above, a POSA would understand this phrase to mean "separating the sperm cells according to whether the cells carry an X or Y chromosome." Ex. 1003 ¶ 55. As discussed above in Claim 1(b), Hagele reported separating the sperm cells based on whether they carry an X or Y chromosome. *Id*. ¶¶ 72-73; *see also* Ex. 1005, Abstract, 295. Hagele also determined the percentage of X- and Y-bearing sperm in each fraction and demonstrated that female cows were inseminated with fractions that were predominantly X- or Y-bearing. Ex. 1005, 295-296, Table 1.

Claim 1(d): inserting at least a portion of said sorted sperm cells into a uterus of said female mammal after an onset of estrus; and

See analysis of Claim 1 (preamble). Hagele specifically discloses that "[c]ows showing estrus (n=21) were randomly inseminated with either X or Y

chromosome-bearing spermatozoa fractions at 12, 24 and 36 h after the onset of estrus." Ex. 1005, 295. A POSA would understand Hagele's disclosure of inseminating cows showing estrus with X- or Y-bearing sperm factions to necessarily mean that Hagele inserted the sex-sorted sperm into the uterus of a female cow. Ex. 1003 ¶ 75.

Claim 1(e): fertilizing a plurality of said eggs to produce at least two sexed embryos of the desired sex from said female mammal.

See analysis of Claim 1 (preamble). As discussed, Hagele presents the results of sexing, by chromosomal analysis, day-12 to day-15 embryos collected from 14 superovulated donors inseminated with semen which had been separated into X- and Y-bearing sperm fractions. Ex. 1005, 295. The results, presented in Table 1, show that "[f]ifty-seven embryos were sexed; 20 from Y chromosome-bearing and 37 from X chromosome-bearing fractions of semen." *Id*., Abstract & 296 (Table 1).

Claim 2: A method of producing multiple, sexed embryos according to claim 1 wherein said creating superovulation is encouraged during the estrus cycle.

See analysis of Claim 1. Additionally, as noted, Hagele took 25 normally cycling cows, 20 to 60 months of age, and induced them to superovulate by administering FSH-P on days nine to 12 of their estrous cycle. Ex. 1005, 295.

Claim 3: A method of producing multiple, sexed embryos according to claim 2 wherein said step of using an ovulatory pharmaceutical comprises the step of injecting said ovulatory pharmaceutical in half days increments between any of days 2 and 18 of said estrus cycle.

See analysis of Claim 1 (preamble) and Claim 2. Additionally, as noted above in the analysis of Claim 1 (preamble), Hagele discloses administering the ovulatory pharmaceutical FSH-P twice daily for 4.5 days on days 9-12 of the cows' estrous cycles. Ex. 1005, 295. Although Hagele only discloses "administering" the FSH-P, and not "injecting" it, a POSA would understand that these drugs are ***only*** available in injectable form, so administration by injection is inherent. Ex. 1003 ¶ 81.

Claim 7: A method of producing multiple, sexed embryos as described in claim 1 wherein said step of using an ovulatory pharmaceutical to cause multiple eggs to be produced comprises the step of injecting a dosage of follicle stimulating hormone a plurality of times a day.

See analysis of Claim 1 (preamble). Additionally, as noted above in the analysis of Claim 3, Hagele discloses administering 5 mg of the ovulatory pharmaceutical FSH-P twice daily (*i.e.*, a "plurality of times a day") for 4.5 days on days 9-12 of the cows' estrous cycle (for a total of 45 mg administered). Ex. 1005, 295. Again, although Hagele only discloses "administering" the FSH-P, and not "injecting" it, a POSA would understand that this drug is ***only*** available in injectable form, so administration by injection is inherent. Ex. 1003 ¶ 83.

Claim 8: A method of producing multiple, sexed embryos as described in claim 7 wherein said step of creating superovulation in said mammal to create at least two eggs further comprises the step of incorporating an estrus manipulation system comprising the step of supplementing said dosage of follicle stimulant hormone with prostaglandin F-2-alpha.

See analysis of Claim 7. As noted, Hagele injected FSH-P twice daily for 4.5 days, totaling nine injections. Ex. 1005, 295. Additionally, Hagele states: "Forty-eight hours after starting superovulation, each cow received 625 ug of cloprostenol (Estrumate, ICI Pharma, Mississauga, Ontario)." *Id*. Estrumate is a well-known PGF-2-alpha analogue. As discussed in Section VII above, the '422 patent uses the term "prostaglandin F-2-alpha" broadly so as to encompass both the naturally occurring PGF-2-alpha, as well as its well-known analogue, Estrumate. Ex. 1003 ¶¶ 60-62, 85 (explaining that Estrumate is the same PGF-2-alpha analogue disclosed in Macmillan, which is expressly incorporated by the '422 patent as exemplary of techniques utilizing PGF-2-alpha to synchronize estrus in cows). As such, Hagele's teaching of supplementing the FSH injections with an injection of Estrumate necessarily discloses this limitation. *Id*. ¶ 85.

C. Ground 2: Claims 3, 7, and 8 Are Obvious Over Hagele In View Of Seidel '91.

Claims 3 & 7:

See analysis of Ground 1, Claims 3 and 7, above. As discussed therein, Hagele expressly discloses each of the limitations of claims 3 and 7, with the exception of "injecting" the ovulatory pharmaceutical, which is inherent. However,

should the Board require an explicit teaching of "injecting" the claimed pharmaceuticals, Seidel '91 (Ex. 1009) expressly discloses this. Ex. 1003 ¶ 86.

Specifically, Seidel '91 discloses that a "generally-accepted" method of superovulating cattle is to administer "eight to ten ***injections*** of follicle stimulating hormone (FSH) subcutaneously (s.c.) or i.m. at half-day intervals." Ex. 1009 at 28 (emphasis added). Seidel '91 also teaches that "[t]he most common FSH regimen is 6, 6, 4, 4, 2, 2, 2, and 2 mg at half-day intervals with prostaglandin F2 alpha given with the sixth or seventh FSH ***injection.***" *Id.* (emphasis added).

Thus, Seidel '91 corroborates what a POSA would already have known: FSH and PGF-2-alpha are only available in injectable form. Ex. 1003 ¶ 86. As such, a POSA would have understood that Hagele's "administration" of these drugs was necessarily by injection. *Id*.

Claim 8:

See analysis of Ground 1, Claim 8, above. As discussed therein, Hagele expressly discloses the step of supplementing the dosage of follicle stimulating hormone (*i.e.*, FSH-P) with prostaglandin F-2-alpha (*i.e.*, Estrumate, a well-known PGF-2-alpha analogue). However, should the Board interpret the term "prostaglandin F-2-alpha" narrowly so as to exclude its well-known analogues, claim 8 would nonetheless be obvious over Hagele alone or in view of Seidel '91. Ex. 1003 ¶ 87.

Specifically, a POSA would have understood that synthetic forms of "prostaglandin F-2-alpha" could have been substituted for natural forms of the drug when supplementing FSH administration to induce superovulation. *Id*. It thus would have been routine and obvious to substitute naturally-occurring prostaglandin F-2-alpha in place of Estrumate, as taught by Hagele. *Id*.

Moreover, if any additional motivation were needed to make this substitution, Seidel '91 expressly discloses that, when dosing with PGF-2-alpha, either the naturally-occurring drug ***or*** an analogue may be used. Ex. 1009, 44 ("In our experience, it is best to give donors a luteolytic dose of prostaglandin F2 alpha, ***or an analogue***, after the flushing procedure.") (emphasis added); *see also id.,* 28, (disclosing that another popular method of superovulation is to administer PMSG "followed by a luteolytic dose of prostaglandin F2 alpha ***or an analogue*** i.m. [intramuscularly] two to three days later.") (emphasis added). Indeed, the interchangeability of natural and synthetic forms of PGF-2-alpha for luteolysis in a superovulation protocol was well known, and thus a POSA would have reasonably expected either form to work equally well. Ex. 1003 ¶ 88.

In view of the above, a POSA would have known from Seidel '91 that "the most common regimen" to superovulate cattle is by injecting FSH at half-day intervals and then, around the sixth or seventh FSH injection, also to inject the cattle with PGF-2-alpha or an analogue. *Id*. ¶ 89. Additionally, the POSA would

have known that PGF-2-alpha analogues (such as Estrumate) also are commonly used in superovulation methods in place of PGF-2-alpha. *Id*. The POSA would have had a reasonable expectation of success in using a method like that taught in Seidel '91 to produce multiple, sexed embryos as Seidel '91 states that "superovulation usually yields an average of six usable embryos." *Id*.; *see also* Ex. 1009, 27.

Accordingly, should Hagele alone be insufficient to anticipate or render obvious claims 3, 7, and 8, then these claims would nonetheless be obvious over Hagele alone or in combination with Seidel '91.

D. Ground 3: Claim 4 Is Obvious Over Hagele In View Of Nowshari and Donaldson.

Claim 4 depends from claim 3 and further requires "injecting at least seven injections" and "incorporating an estrus manipulation system at least on about the sixth and seventh injections." As detailed in Ground 1, Claim 3 above, Hagele expressly discloses administering FSH twice daily for 4.5 days, totaling nine injections. Ex. 1005, 295. Hagele also expressly discloses co-administering Estrumate (a well-known PGF-2-alpha analogue) after the start of superovulation, which would correspond to the sixth or seventh injection of FSH. Ex. 1003 ¶ 91 (explaining that 48 hours post-superovulation corresponds to the sixth, or possibly the seventh, injection of FSH). However, Hagele does not expressly teach a ***second*** administration of PGF-2-alpha.

Nonetheless, administering multiple injections of PGF-2-alpha along with FSH would have been obvious. *Id*. ¶¶ 92-95. For example, Nowshari (Ex. 1016) and Donaldson (Ex. 1017) both teach methods of superovulating mammals by co-administering FSH and PGF-2-alpha. *Id*. Specifically, Nowshari superovulated 64 female goats with injections twice-a-day injections of FSH at 4, 4, 2, 2, 2 and 2 mg. Ex. 1016, 798. "Along with the last 2 injections [of FSH], the goats received 5 mg PGF2α." *Id*. Thus, Nowshari teaches co-administering PGF-2-alpha on the fifth and sixth injections of FSH, *i.e.*, on "***about*** the sixth and seventh injections." Ex. 1003 ¶ 93.

Similarly, Donaldson superovulated cows with twice-a-day injections of FSH at 6, 6, 4, 4, 2, 2, 2, and 2 mg. Ex. 1017, 35. "[O]n day three" of the FSH injections, Donaldson co-administered three injections of PGF-2-alpha (at morning, noon, and night). *Id*. The morning and night-time injections of PGF-2-alpha would have corresponded to the fifth (morning) and sixth (night) injections of FSH. *See id.* Thus, like Nowshari, Donaldson also teaches co-administering PGF-2-alpha on the fifth and sixth injections of FSH, i.e., on "***about*** the sixth and seventh injections." Ex. 1003 ¶ 94.

Because the factors affecting a mammal's estrous cycle were well known in December 1997, and were discussed by Hagele, Nowshari, and Donaldson, optimization of superovulation treatment by adjusting the timing and interval of

co-administration of FSH and PGF-2-alpha would have been both obvious and well within the skill of a POSA. Ex. 1003 ¶ 95. Moreover, a POSA would have reasonably expected to successfully use the superovulation techniques taught by Hagele (as modified by Nowshari and Donaldson to include a second PGF-2-alpha injection) to produce multiple, sexed embryos given Hagele's results. *Id*.

E. Ground 4: Claims 1-4, 7-8, 10, 13 And 14 Are Obvious Over Hagele In View Of Spaulding.

Claim 10 depends from claim 1 and further recites that the sperm cells are stained, sorted at a rate above 500 sorts per second, and concentrated. Claim 13 recites a method of producing a mammal of a desired sex using the processes described in claim 1. Claim 14 depends from claim 13 and further recites sorting sperm cells at a rate above 500 sorts per second and producing a sexed sperm cell specimen.

Each of these claims is obvious over Hagele in view of Spaulding (Ex. 1010).[4] Ex. 1003 ¶¶ 97-126.

[4] Additionally, should the PTAB conclude that claims 1-3 and 7-8 are not anticipated by Hagele for any reason, then these claims would nonetheless be obvious over Hagele in view of Spaulding for all the reasons discussed in Ground 1 combined with the reasons discussed in Ground 4.

Claim 10 (preamble): A method of producing multiple, sexed embryos as described in claim 1 and further comprising the steps of:

See analysis of Ground 1. As discussed, Hagele discloses a method of producing multiple sexed embryos. Ex. 1005, Abstract, 294-296, Table 1. More specifically, Hagele sex-sorts bovine sperm cells using a sedimentation-galvanization cell in which X- and Y-bearing sperm migrate toward cathodic and anodic chambers, respectively, are collected, centrifuged, and washed. *Id.*, 295. Hagele then corroborates that the sperm have been sorted using quinacrine mustard staining, which produces anterior fluorescing bodies[5] in Y-bearing sperm but not X-bearing sperm fractions. *Id.*, 294-295. Next, Hagele collects the sex-sorted sperm and inseminates female cows to produce multiple, sexed embryos. *Id.*, Abstract, 294-295.

Claim 10 (a): staining sperm cells of a male mammal;

See analysis of Ground 1. Moreover, as noted above, after using sedimentation galvanization to sex-sort the bovine sperm, Hagele evaluates the separation with quinacrine mustard staining, which produces anterior fluorescing bodies ("B-bodies") in Y-bearing sperm but not X-bearing sperm fractions. *Id.*, 295-296, Table 1. Thus, Hagele expressly meets this limitation.

[5] Hagele refers to the anterior fluorescing bodies referred to as "B-bodies," though they are also commonly referred to in the art as "F-bodies" in non-bovine species. Ex. 1003 ¶ 98.

Additionally, Hagele specifically notes the use of flow cytometry as a means of measuring DNA content differences between X- and Y-bearing sperm:

> Therefore, in these animals [*i.e.*, bulls], evaluation of the success of separation methods would appear to have to rely on either ***the new technique of flow cytometry***, which measures differences in DNA content of X and Y chromosome-bearing spermatozoa in bull, boar and ram semen (14), or the more conventional basis of determining the sex ratio by progeny sexing.

Id., 295 (emphasis added). Elsewhere, Hagele states that, "[a]t present, the only practical method, apart from progeny sexing, for determining whether spermatozoa with B-bodies are also Y chromosome-bearing is by flow cytometry after fluorescent staining of DNA (26)."[6] *Id.*, 297.

Thus, in 1984 when Hagele published, a POSA would have been aware that flow cytometry could be used to measure the DNA content of sperm. Of course, by the early 1990s, thanks in large part to the work of Lawrence Johnson and others, this technique had become the preferred means of distinguishing X- and Y-bearing mammalian sperm based on detectable differences in DNA content. Ex. 1003 ¶ 102. One reference that discloses flow cytometry to sex-sort mammalian sperm is Spaulding, which issued in 1991. Ex. 1010. Spaulding, like XY's own work,

[6] The two references cited by Hagele, references 14 and 26, are both co-authored by Lawrence A. Johnson, the principal inventor of using flow cytometry to sex-sort semen, and from which XY's own patents largely derive.

borrows heavily from Lawrence Johnson's pioneering work. *Id*. In Spaulding's method—as in virtually every other modern method for flow-sorting sperm—the sperm cells are ***stained with Hoechst 33342 dye***. *Id*.; *see also id.*, 9:41-42 ("We sorted the sperm based on total DNA content as measured with the aid of the Hoechst dye.").

Thus, by the early 1990s, a POSA reading Hagele would have been well aware of Spaulding's more advanced flow cytometry method of sex-sorting sperm cells, and would have been highly motivated to substitute that method in place of Hagele's more rudimentary sedimentation galvanization method of sex-sorting. Ex. 1003 ¶ 103. Indeed, by 1991 the POSA would have known very well that flow cytometry was the single best way to sex-sort sperm. *Id*. As such, it would have been plainly obvious for a POSA utilizing Hagele's method of superovulation to substitute the flow cytometric method of Spaulding in place of the sedimentation galvanization technique taught by Hagele. *Id*.

The United States Supreme Court has held:

> When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would

> improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 417 (2007).

Here, design incentives and other market forces—namely, the recognized need in the art to improve the process of producing offspring of a desired sex in agriculturally important food animals, such as cattle—would have prompted a POSA to experiment with Hagele's method to look for ways of improving upon it. Ex. 1003 ¶ 104. One obvious way would have been to use the recent advances in flow cytometry taught by Spaulding to produce the sample of sex-sorted sperm. *Id*. The POSA also would have had a reasonable expectation of success in using the flow-cytometry method of Spaulding in producing multiple, sexed embryos as Spaulding discloses that its flow-cytometry method was able to successfully sort sperm. *Id*. (citing Ex. 1010 at 9:39-10:8). Additionally, Hagele taught that inseminating superovulated mammals with sorted sperm produced multiple, sexed embryos. *Id*. (citing Ex. 1005, Abstract, 294-296, Table 1).

In sum, it would have been obvious, based on Hagele's teaching, to use the improved flow-cytometry techniques taught in Spaulding for sex-sorting mammalian sperm. Ex. 1003 ¶ 105. In doing so, the sperm of a male mammal would have necessarily been stained with a dye prior to sorting. *Id*.

Claim 10(b): sorting according to said sex of said sperm cells at sperm cell sorting rates selected from the group consisting of: above 500 sorts per second, above 1000 sorts per second, and above 1200 sorts per second;

As an initial matter, since the three recited ranges of sort speeds are presented in *Markush* format, the prior art need only disclose one of the members of the group to read on this limitation. *See*, *e.g.*, *In re Goodman*, 11 F.3d 1046, 1053 (Fed. Cir. 1993) (explaining that generic claims are anticipated by species); *In Re Gosteli*, 872 F.2d 1008, 1010 (Fed. Cir. 1989) (affirming anticipation rejection of *Markush* claims where prior art disclosed species falling within one or more of the claimed groups). In this case, the broadest range is "above 500 sorts per second." Accordingly, Petitioner directs its invalidity arguments to this range.

As discussed in Ground 1 above, Hagele sex-sorts bovine sperm cells using a sedimentation-galvanization cell in which X- and Y-bearing sperm migrate toward cathodic and anodic chambers, respectively, are collected, centrifuged, and washed. Ex. 1005, 295. Hagele, however, does not disclose the speed at which the sperm are sorted in this process. However, as detailed above in Ground 4, Claim 10(a), a POSA would have known by the early 1990s that flow cytometry was the preferred technique for evaluating and sorting sperm. Ex. 1003 ¶ 107. To that end, the POSA would have looked to Spaulding, which disclosed improved methods and instruments for sorting sperm via flow cytometry. *Id*.; *see also* Ex. 1010.

Like Hagele, Spaulding carried out mammalian sperm sorting. Ex. 1010, Abstract. However, unlike Hagele, Spaulding utilized a modified, commercially-available flow cytometer—the Epics® Model 752 Flow Cytometer.[7] *Id.*, 7:52-56 (Example I). Spaulding made numerous modifications to the cytometer to speed up sort rates and improve both resolution and yield, including:

- placing the instrument on a fixed rigid tubular frame table equipped with double detection shear/compression mounts;
- improving flow cytometer resolution by continuously degassing the sheath fluid during the sort;
- using a sample insertion tube whose tip was bilaterally beveled and polished to a 20° angle, thus creating a ribbon-shaped sample stream whose flat surface is normal to the long axis of the laser beam;
- modifying the electronics and the optics; and
- modifying the laser, air-flow, and room temperature.

Id., 7:42-10:8 (Example I).

In preparation for sorting, the sperm cells were washed, concentrated by centrifugation, resuspended and diluted to a cell concentration of 20 x 10^6 cells/ml, and then stained with Hoechst 33342 dye for at least two hours. *Id.*, 8:15-32.

[7] Spaulding specifically notes that "one can make similar modifications to other flow cytometers." *Id.*, 7:57-58.

Next, the sperm were sorted on the modified Epics® Model 752 Flow Cytometer. *Id.*, 8:37-40. Spaulding explains the flow cytometry process:

> The flow cytometer utilizes a laser to interrogate a sample stream of suspended cells contained within an outer sheath fluid. For DNA analysis, these cells are bound with a dye which, in response to ultraviolet laser excitation, emits fluorescent light in proportion to the amount of DNA. … Depending on the amount of DNA detected, one can then separate cells into one of three containers (X, Y, or waste) employing the flow cytometer sorting capability. In this operation, an ultrasonic vibrator breaks the sample stream into individual droplets, each containing an individual cell. The droplets are given a charge based on the DNA content of the cell and are deflected into the appropriate container by an electric field.

Id., 7:60-8:7.

Using the modified Epics® Model 752 Flow Cytometer, Spaulding states the "instrument is capable of ***analyzing and sorting cells at rates up to 10,000 cells/second***." *Id.*, 8:7-8 (emphasis added). Moreover, in Example I, Spaulding reports whole sperm analysis rates "up to 10,000 cells per second" and X-enriched and Y-enriched collection rates "between 100 and ***500 cells/sec***." *Id.*, 9:46-52 (emphasis added). Spaulding also notes, however, that "[t]he actual flow rate used in any sort depends on the state of the machine, with a reduction in flow rate required to improve resolution." *Id.*, 9:52-55.

As Hagele discloses using sex-sorted sperm to produce sexed embryos, and as Spaulding discloses an improved method of obtaining sex-sorted sperm (namely, through use of flow cytometry), a POSA would have naturally looked to combine these two teachings. Ex. 1003 ¶ 113. More specifically, a POSA practicing Hagele's method of fertilizing superovulating cows with sex-sorted bovine sperm would have sought to utilize flow cytometry as an alternative means of obtaining enriched subpopulations of sex-sorted bull sperm. *Id*. That POSA would have looked to Spaulding, which touted methods and instruments capable of improving the yield and speed of flow-sorting sperm cells. *Id*.

Further, the POSA would not only have been motivated to use Spaulding's improved flow cytometry techniques, but also would have reasonably expected Spaulding's modified flow cytometer to be "capable of analyzing and sorting cells at rates up to 10,000 cells/second."[8] Ex. 1010, 8:7-9. Additionally, in Example 1, Spaulding reports ***collecting*** up to ***500*** X-bearing or Y-bearing sperm per second

[8] This is true even if Spaulding's instrument were, in practice, not able to sort at those speeds. *See*, *e.g.*, *Beckman Instruments v. LKB Produkter AB*, 892 F.2d 1547, 1551 (Fed. Cir. 1989) (explaining that a prior art reference "is prior art for all that it teaches").

and, further, suggests that it could have improved the collection rate, albeit at the cost of decreased resolution.[9] *Id.*, 9:48-55.

As such, Hagele in view of Spaulding renders obvious sorting sperm at speeds greater than 500 sperm cells per second. Ex. 1003 ¶¶ 113-116. What's more, even if Spaulding is deemed only to disclose speeds of up to 500—that is, if Spaulding's generic disclosure of "sorting cells at rates up to 10,000 cells/second" is ignored or deemed non-enabling—it ***still*** would have been obvious to sort at speeds greater than 500 sperm cells per second, as such is explicitly taught by Spaulding Example 1. *Id.* ¶¶ 114-116. A POSA would have both desired to do so and would have reasonably expected such sort speeds to be feasible. *Id*. ¶ 116; *see also In re Geisler*, 116 F.3d 1465, 1469-71 (Fed. Cir. 1997) (prior art disclosure of "not less than about [100 Angstroms]" rendered obvious claim reciting thickness of "50 to 100 Angstroms."); *see also In re Ethicon*, *Inc*., 844 F.3d 1344, 1351 (Fed. Cir. 2017) (explaining that "[t]he normal desire of artisans to improve upon what is already generally known can provide the motivation to optimize variables"); *Gentiluomo v. Brunswick Bowling and Billiards Corp.*, 36 Fed. App'x 433, 438

[9] Notably, the '422 patent claims have no resolution or purity requirement. Accordingly, even if increasing the sort speed in Example 1 of Spaulding would have led to decreased resolution or lower yields of X and Y-bearing sperm, such would still have been within the scope of the '422 patent claims. Ex. 1003 ¶ 115.

(Fed. Cir. 2002) (non-precedential) (noting that overlapping ranges are not required to find a claim *prima facie* obvious).

Claim 10(c): concentrating said sorted sperm cells.

Concentrating a cell population after sex-sorting is conventional in preparation for many subsequent procedures. Ex. 1003 ¶ 117. This is typically done by centrifuging the cells and resuspending to a desired concentration. *Id*.; *see also* Ex. 1001, 13:39-14:2 (explaining that a desired sort concentration is accomplished "through the use of centrifugation after which the sheath fluid and preserving fluid may be removed" and then "a final extension" added to bring the concentration to the desired level). Virtually all sex-sorting methods involve concentrating the sorted sperms to a desired concentration. Ex. 1003 ¶ 117.

Indeed, Hagele expressly discloses concentrating the sorted sperm cells:

> Spermatozoa from ejaculates which showed spermatozoa migration into both anodic (Y chromosome-bearing) and cathodic (X chromosome-bearing) chambers of the sedimentation galvanization cell were ***collected, centrifuged and washed free of the particle-free extender by centrifugation and drawing off the supernatant fluid.*** They were then resuspended in egg yolk-citrate extender to give approximately 20 million motile spermatozoa per 0.5 mL.

Ex. 1005, 295 (emphasis added). Hagele thus discloses what would have already been quite obvious to a POSA: after the sperm are sorted, they should be collected

and concentrated to the desired concentration. Ex. 1003 ¶ 118. Further, a POSA would have reasonably expected to do so because such was routine in the art. *Id*.

Claim 13: A method of producing a mammal of a desired sex using the processes as described in claim 1.

See analysis of Ground 1 above. As discussed therein, Hagele pharmaceutically induced over two dozen cows into superovulating on days nine to 12 of their estrous cycles, inseminated them with sex-sorted sperm, and produced multiple sexed embryos. Ex. 1005, 294-295, Table 1; *see also id.*, Abstract ("Fifty-seven embryos were sexed; 20 from Y chromosome-bearing and 37 from X chromosome-bearing fractions of semen."). Notably, Hagele recovered the embryos on days 12 to 15 after onset of estrus as "hatched blastocysts," at which point several of the sexed embryos were "approximately 2-3 cm in length." *Id.*, 295. The embryos were then fragmented and cultured so that Hagele could perform chromosomal analysis. *Id*. Accordingly, Hagele did not allow the pregnant cows to carry the embryos to term, thus giving birth to "mammals of a desired sex."

Nonetheless, such would have been obvious. Ex. 1003 ¶ 121. Indeed, had Hagele merely fed the pregnant cows for several more months, they presumably would have given birth to either male or female calves, depending on whether they were the product of an X-sexed embryo or a Y-sexed embryo. *Id*. Indeed, as Dr. Miller explains, the whole ***point*** of sex-sorting mammalian sperm is, ultimately, to produce mammals of a desired sex. *Id*. Indeed, Hagele explains that "[t]here would

be ***obvious*** advantages to altering the sex ratio in food producing animals," such as cows. Ex. 1005, 294 (emphasis added). Thus, despite the fact that Hagele itself does not disclose birthing calves of a desired sex, it would have been "obvious"—to use Hagele's word—to employ the methods set forth therein to do so. Ex. 1003 ¶ 121.

Moreover, even if it were not "obvious" to a POSA reading Hagele to "produc[e] a mammal of a desired sex" using Hagele's sexed embryos, the POSA need only look to Spaulding. *Id*. ¶ 122. Indeed, Spaulding's principal object was this very result:

> Various methods have been proposed for modifying mammalian semen ***to increase the relative percentage of X- or Y-sperm*** in a semen sample, and thereby achieve a ***greater likelihood of female or male offspring***.
>
> * * *
>
> It is an object of this invention to provide methods to ***increase the probability that mammalian offspring will be of a desired sex*** or carry a gene for a particular sex chromosome linked trait.

Ex. 1010, 1:37-40, 4:16-19 (emphases added). Thus, a POSA reading Hagele in view of Spaulding would have understood that the end goal of producing multiple, sexed embryos is to produce mammals of a desired sex. Ex. 1003 ¶ 122.

Finally, it bears pointing out that, like Hagele, the '422 patent fails to disclose mammals produced according to the methods disclosed therein. Rather,

like Hagele, the '422 patent merely discloses the production of sexed embryos, and does not report the births of any live mammals. Accordingly, to the extent the '422 patent's disclosure of producing sexed embryos supports its claims to mammals resulting therefrom—which Petitioner does not dispute—then Hagele's similar disclosure necessarily renders those same claims obvious. *See*, *e.g.*, M.P.E.P. § 2163I.A , 2014 WL 11173057 ("The Federal Circuit has pointed out that under United States law, a description that does not render a claimed invention obvious cannot sufficiently describe the invention for the purposes of the written description requirement of 35 U.S.C. 112.").

Claim 14 (preamble): A method of producing a mammal of a desired sex as described in claim 13 wherein said step of sorting comprises the steps of:

See analysis of Ground 4, Claim 13. As discussed above, it would have been obvious to use Hagele's method of producing multiple, sexed embryos to go one step further and permit the sexed embryos to be carried to term, thereby leading to a calf of a desired sex. Ex. 1003 ¶ 124. Moreover, Spaulding provides additional motivation, as it explains that an object of sex-sorting mammalian sperm is to "increase the probability that mammalian offspring will be of a desired sex." Ex. 1010, 4:16-19.

Claim 14(a): sorting said sperm cells at sperm cell sorting rates selected from the group consisting of: above 500 sorts per second, above 1000 sorts per second, and above 1200 sorts per second; and

See analysis of Ground 4, Claim 10(b). As discussed above, Hagele proposes utilizing flow cytometry, and Spaulding provides improved flow cytometry methods and instruments. In addition, Spaulding provides an explicit teaching of a modified flow cytometer "capable of analyzing and sorting cells at rates up to 10,000 cells/second." Ex. 1010, 8:7-9. Spaulding also reports specifically collecting up to 500 X-bearing or Y-bearing sperm per second and suggests that even faster sort speeds are easily achieved. *Id.*, 9:48-55. Accordingly, Hagele in view of Spaulding teaches or suggests sorting sperm at speeds greater than 500 sperm cells per second. Ex. 1003 ¶ 125.

Claim 14(b): producing a sexed sperm cell specimen.

As discussed in Section VII above, a "sexed sperm cell specimen" is simply a sample of sperm that has been selected to be either X- or Y-bearing and prepared to the desired dosage level. Ex. 1003 ¶ 63. This limitation is necessarily met by virtually any sample of sorted sperm cells produced according to claim 1, which must "fertiliz[e] a plurality of said eggs to produce at least two sexed embryos of the desired sex from said female mammal." *Id*. ¶ 126. Thus, the sorted bovine sperm samples taught in Hagele, which were used to successfully fertilize multiple eggs in superovulated cows, constitute a "sexed sperm cell specimen." *Id*.

F. Ground 5: Claims 10 And 14 Are Obvious Over Hagele In View Of Spaulding And In Further View Of Rens.

As discussed in Ground 4 above, claims 10 and 14 each depend from claim 1 and further require that the sperm cells be sorted at a rate "above 500 sorts per second." Hagele in view of Spaulding renders these claims obvious for the reasons discussed in Ground 4. However, should any additional motivation/teaching be required to sort at speeds above 500 sorts per second, Rens provides it in abundance. Ex. 1003 ¶¶ 127-132.

Like Spaulding, Rens builds upon Johnson's method of flow-sorting sperm by increasing the sort speed of Johnson's method. Ex. 1014, 2:22-42, 4:43-49. More specifically, Rens discloses "a high speed sorter" modified with an elliptical-shaped nozzle designed to orient and sort sperm in a way so as to increase sort speed yet maintain high sort purity. *Id.*, 2:22-42. Notably, Rens tested its elliptical-shaped nozzle with two commercially-available cell sorters: an Epics® V Series flow cytometer/cell sorter and a MoFlo® high speed cell sorter. *Id*., 5:12-18. Rens reports that the high-speed sorters modified with the elliptical nozzle "increase[] the yield of sorted X- and Y-chromosome bearing sperm 10-fold." *Id.*, 4:43-48; 5:13-18. According to Rens, "with the elliptical nozzle, the proportion of proper orientation is maintained at sample rates up to ***at least 15,000 sperm per second***. This high level of performance is beneficial for ***efficient sperm sorting***." *Id.*, 4:29-33 (emphasis added).

In Example 7, Rens applies "the MoFlo® high speed cell sorter" to the flow-cytometry method disclosed in Johnson '86 (Ex. 1012). Ex. 1014, 5:16-20 (explaining that "the MoFlo® high speed cell sorter … was modified for sorting sperm as described in" Johnson '86). Rens Example 7 states that "up to 25 millionxsperm [*sic*] (50 million, total X and Y) were required to be sorted between 9am and 4pm." Ex. 1014, 7:52-54. Example 7 thus reports sorting 1,984 X- and Y-bearing sperm cells per second (*i.e.*, 50 million X- and Y-bearing sperm divided by seven hours).[10] *Id.*; *see also* Ex. 1003 ¶ 129.

Thus, Rens provides both the motivation and the means for sorting sperm at speeds greater than 500 sorts per second. *Id*. ¶ 130. Indeed, the PTAB has previously held ***exactly this***. Specifically, in IPR 2014-01161 (Ex. 1019), the PTAB found that a POSA would have been motivated to utilize Rens' high-speed sorter in prior art sperm-sorting methods specifically to improve the efficiency of sperm sorting:

[10] In IPR 2014-01161, the Patent Owner, XY, took the (ultimately unavailing) position that Rens Example 7 achieves a sort rate of only 992 X or Y sorts per second, not 1,984 sorts per second. Ex. 1019, 18-19. The PTAB rejected the Patent Owner's narrow reading of the phrase "sorts per second." *Id*., 10-12, 18-19. But even if the Patent Owner's strained interpretation of "sorts per second" were adopted in this case, it would be irrelevant as 992 sorts per second is still nearly ***double*** that recited in claims 10 and 14.

A skilled artisan would have been looking for ways to increase the sort rate of Johnson's method. At the time of the invention, a person of ordinary skill in the art would have been well aware of the desirability of sorting X and Y sperm at increasingly higher sort rates to facilitate sex-specific artificial insemination. The commercial importance of gender selection in animal offspring was well understood; for example, in "beef cattle and sheep breeds, the male grows at a faster rate than the female and hence is preferred for meat production," while "sexed semen to produce only females would make milk production more efficient." [Johnson '92, Ex. 1007], 1:15-24. At the time of the invention, a well-established goal in the field was "the utilization of high speed cell sorters in order to maximize the number of sorted sperm per unit time." [Rens, Ex. 1014], 2:40–43.

The ['422 patent] inventors acknowledge that artisans were actively seeking ways to increase the rates of sorting X and Y sperm at the time of the invention, and indicate that "[a]dvances have been particularly made by the flow cytometers available through Cytomation, Inc. under the MoFlo® trademark," which the inventors further characterize as having "increased sorting speeds extraordinarily and have thus made flow cytometry a technique which is likely to make feasible the commercial application of sperm sorting." Ex. 1001, 7:3–9; *see id.* at 2:9–22 (although "still experimental, separation has been significantly enhanced" by using "high speed flow cytometers such as the MoFlo® flow cytometer produced by Cytomation, Inc.," which produce "almost ten-fold

> advances in speed" of sorting sperm cells). Artisans were aware that "the time critical nature of" sperm cells in the artificial insemination process "made speed an essential element in achieving high efficacy and success rates." *Id*. at 2:27–29. A desire to achieve higher sort rates would have prompted a skilled artisan to look for ways to modify Johnson's method to increase the rate of sorting.

Ex. 1019, 19-20; *see also id.*, 17 (finding it "significant that Rens uses a MoFlo® high speed cell sorter, which the '920 patent specification credits as having 'increased sorting speeds extraordinarily' to achieve 'rates of sorting in the thousand and twelve hundred ranges.'"); *id*. ("A person of ordinary skill in the art would have been aware of the orienting nozzle disclosed in Rens, and would have recognized its 'application for sorting viable male (Y) and female (X) sperm populations in a cell source.' [Rens, Ex. 1014] at Abstract.").[11]

Further, Example 7 of Rens demonstrated successful insemination of cattle using sperm sorted by Rens' high-speed sorting method. Ex. 1014, 7:48-57 (Example 7); *see also* Ex. 1019, 21 (holding that Rens indicates that the

[11] In IPR 2014-01161, the Board found the challenged claims of U.S. Patent No. 7,195,920—which shares common inventorship and priority with the '422 patent—to be unpatentable over a combination of references that include Johnson '92 and Rens. Ex. 1019. The relevant portions of the '920 patent cited by the PTAB in the foregoing quoted passages are identical to those contained in the '422 patent. As such, the PTAB's reasoning applies equally well to the '422 patent.

fertilization experiments of Example 7 "were successfully carried out 5 times"). As such, a POSA also would have reasonably expected Rens' high-speed sorter to work just fine in performing the sorting step recited in claims 10 and 14. Ex. 1003 ¶ 132; *see also* Ex. 1019, 21 ("A preponderance of evidence shows that a skilled artisan would have had the desire and ability to carry out the method of claim 1 with a reasonable expectation of success.")

Thus, a POSA, informed by the combined disclosures of the cited prior art, would have had the desire and ability, with a reasonable expectation of success, to modify Hagele's fertilization method with the flow-sorting method taught by Spaulding as modified (if necessary) by Rens to "sort[] according to said sex of said sperm cells at sperm cell sorting rates selected from … above 500 sorts per second." Ex. 1003 ¶ 133.

G. Ground 6: Claims 13 And 14 Are Obvious Over Hagele In View Of Johnson '92 And In Further View Of Spaulding.

As discussed above, claims 13 and 14 require "producing a mammal of a desired sex using the processes as described in claim 1." These claims are obvious over Hagele in view of Spaulding for the reasons detailed in Ground 4. However, should additional motivation be required to arrive at the invention recited in claims 13 and 14, Johnson '92 provides more than enough. Ex. 1003 ¶¶ 134-138.

Johnson '92 begins by explaining the numerous benefits to producing sex-selected mammals:

> Gender of animal offspring is important to livestock producers. Because the dairy farmer has little use for most bull calves, the use of sexed semen to produce only females would ***make milk production more efficient.*** Swine farmers would ***produce pork more efficiently*** if they were able to market only female swine, because females grow faster than males.
>
> In beef cattle and sheep breeds, the male grows at a faster rate than the female and hence is preferred for ***meat production.***
>
> In addition, the ability to specify male or female offspring should ***shorten the time required for genetic improvements***, since desirable traits are often associated with one or the other parent.

Ex. 1007, 1:14-29 (emphasis added).

To that end, Johnson '92 details methods of producing mammals of a desired sex by inseminating a female with sperm that has been sorted using flow cytometry techniques. *Id.*, 2:64-6:14. It concludes with several examples, including Example 4, in which the sex-sorting techniques described in the previous examples were used to sort porcine sperm. *Id.*, 7:35-41. The sperm cells were then inserted into females, producing a litter of 18 piglets. *Id*. In the litter produced using X-sorted sperm, 88% of the resulting piglets were female; in the litter produced using Y-sorted sperm, 67% of the resulting piglets were male. *Id*.

Accordingly, Johnson '92 provides both the motivation to produce sex-selected mammals, as well as a reasonable expectation of success. Ex. 1003 ¶

137. It thus would have been even more obvious to modify Hagele's method of superovulating cattle by using sperm sex-sorted using the flow cytometric techniques taught in Johnson '92. *Id*. As such, claim 13 would have been obvious over Hagele and Johnson '92. *Id*.

Further, it also would have been obvious to improve the sort speed of the sex-sorting method, such as by using the modified flow cytometer taught by Spaulding, which is "capable of analyzing and sorting cells at rates up to 10,000 cells/second." Ex. 1010, 8:7-9; *see also* Ex. 1003 ¶ 138.

In sum, Hagele in view of Johnson '92 and Spaulding renders obvious claims 13 and 14.[12]

IX. CONCLUSION

For the foregoing reasons, Petitioner respectfully requests that trial be instituted and that claims 1-4, 7-8, 10, and 13-14 of the '422 patent be cancelled.

[12] Moreover, should any additional motivation be needed to arrive at the "above 500 sorts per second" recitation of claim 14, Rens could be used, as detailed in Ground 5 above. If the Board determines that this is necessary, Petitioner proposes an additional Ground of unpatentability as to claim 14 only: Hagele in view of Johnson '92 and Spaulding and in further view of Rens.

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CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION

Pursuant to 37 C.F.R. § 42.24, I certify that the foregoing **PETITION FOR *INTER PARTES* REVIEW** contains 12,835 words (as calculated by the word processing system used to prepare the Petition), excluding the parts of the Petition exempted by 37 C.F.R. § 42.24(a)(1).

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CERTIFICATE OF SERVICE ON PATENT OWNER

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), I hereby certify that on this 4th day of December, 2017, true and correct copies of this PETITION FOR *INTER PARTES* REVIEW, and all Exhibits thereto**,** were served by overnight courier service at the following address for the Patent Owner:

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