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Attorneys for Plaintiffs
KYOWA HAKKO KIRIN CO., LTD. and
BIOWA, INC.

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

KYOWA HAKKO KIRIN CO., LTD. and
BIOWA, INC.,

Plaintiffs,

v.

ARAGEN BIOSCIENCE, INC. and
TRANSPOSAGEN BIOPHARMACEUTICALS,
INC.,

Defendants.

Case No. _____

**COMPLAINT FOR PATENT
INFRINGEMENT**

DEMAND FOR JURY TRIAL

Plaintiffs Kyowa Hakko Kirin Co., Ltd. (“KHK”) and BioWa, Inc. (“BioWa”) (together, “Plaintiffs”) for their complaint against Aragen Bioscience, Inc. (“Aragen”) and Transposagen Biopharmaceuticals, Inc. (“Transposagen”) (together, “Defendants”), state and allege as follows:

THE PARTIES

1
2 1. KHK, a research-based life sciences company with special strengths in
3 biotechnology, is a corporation organized under the laws of Japan, with its principal place of
4 business in Tokyo, Japan.

5 2. BioWa, a wholly owned subsidiary of KHK, is a corporation organized under the
6 laws of Delaware, with its principal place of business in Princeton, New Jersey.

7 3. On information and belief, Aragen is a corporation organized under the laws of
8 California, with its principal place of business in Morgan Hill, California. On information and
9 belief, Aragen is engaged in the business of developing, offering to sell, and selling its products
10 and services to companies and research institutions throughout the United States, including the
11 State of California.

12 4. On information and belief, Transposagen is a corporation organized under the laws
13 of Delaware, with its principal place of business in Lexington, Kentucky. On information and
14 belief, Transposagen is engaged in the business of developing, offering to sell, and selling its
15 products and services to companies and research institutions throughout the United States,
16 including the State of California.

JURISDICTION AND VENUE

17
18 5. This action arises under the Patent Act, 35 U.S.C. § 271 *et seq.* This Court has
19 original jurisdiction over this controversy pursuant to 28 U.S.C. §§ 1331 and 1338.

20 6. Venue in this judicial district is proper under 28 U.S.C. § 1391(b) and (c) and/or
21 28 U.S.C. § 1400(b).

22 7. Personal jurisdiction over Aragen is proper because Aragen is domiciled in
23 California, has substantial business in California, and has purposefully availed itself of the rights
24 and privileges of conducting business in California.

25 8. Personal jurisdiction over Transposagen is proper because Transposagen has
26 purposefully availed itself of the rights and privileges of conducting business in California,
27 including but not limited to its publicized partnership with Aragen relating to the Defendants'
28 infringing activities, described in further detail below.

9. Each of Defendants has infringed and/or continues to infringe, directly and indirectly, the Patents-in-Suit, identified below, in this district.

THE PATENTS-IN-SUIT

10. KHK is the owner of U.S. Patent No. 6,946,292 (the “’292 Patent”), titled “Cells producing antibody compositions with increased antibody dependent cytotoxic activity,” which issued on September 20, 2005. A true and correct copy of the ’292 Patent is attached hereto as Exhibit 1.

11. KHK is the owner of U.S. Patent No. 7,425,446 B2 (the “’446 Patent”), titled “Antibody composition-producing cell,” which issued on September 16, 2008. A true and correct copy of the ’446 Patent is attached hereto as Exhibit 2.

12. KHK is the owner of U.S. Patent No. 8,067,232 (the “’232 Patent”), titled “Antibody composition-producing cell with inactivated A-1,6 fusocyltransferase,” which issued on November 29, 2011. A true and correct copy of the ’232 Patent is attached hereto as Exhibit 3.

13. KHK has granted BioWa an exclusive license under the ’292, ’446, and ’232 Patents.

STATEMENT OF FACTS

Background of Technology at Issue

14. A cell line is a culture of cells developed from a single cell and therefore consisting of cells with a uniform genetic makeup. Cell lines represent a major research tool used in cellular and molecular biology, providing excellent model systems for studying the normal physiology and biochemistry of cells (*e.g.*, metabolic studies, aging), the effects of drugs and toxic compounds on the cells, and mutagenesis and carcinogenesis. Cell lines also are used in drug screening and development, as well as large scale manufacturing of biological compounds (*e.g.*, vaccines, therapeutic proteins). The major advantage of using cell lines for any of these applications is the consistency and reproducibility of results that can be obtained from using a batch of cells with identical genetic make-up.

15. Chinese Hamster Ovary (CHO)-cell-derived cell lines have become a very popular research tool in the molecular biology community. Following their introduction in the 1950s,

1 CHO cells have become useful for many research purposes, and many types of CHO cell lines are
2 in use today. One such cell line is comprised of CHO DG44 cells, which are optimized for
3 certain properties relating to protein expression. CHO cell lines are a mammalian cell model and
4 research tool commonly used in basic academic studies, as well as in medical and pharmaceutical
5 research. CHO cell lines also can be used for commercial purposes to manufacture therapeutic
6 recombinant proteins in a variety of sectors, including basic research, cosmetics, biotechnology,
7 pharmaceutical, vaccine production, human diagnostics, and others.

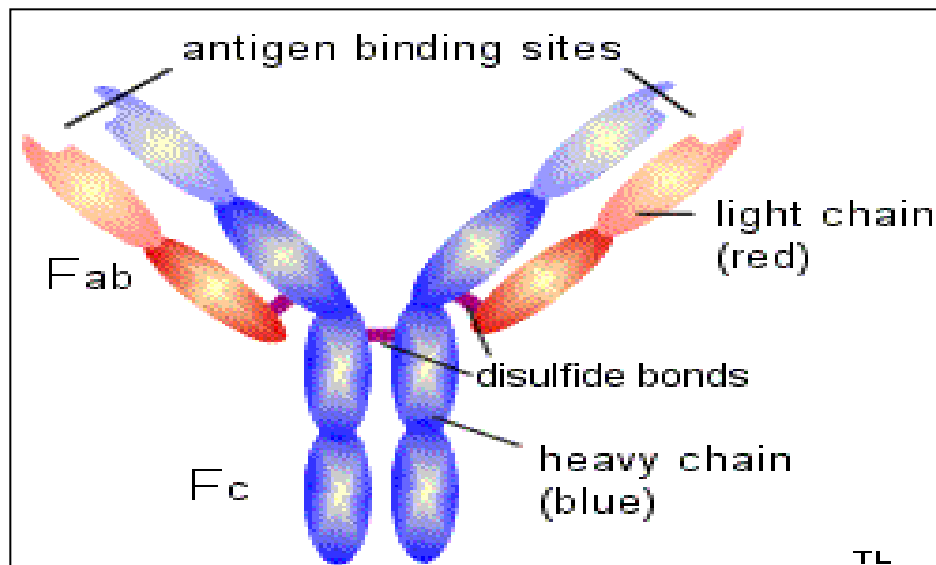
8 16. Among other things, CHO cell lines can be used to produce glycoproteins.
9 Glycoproteins are molecules that consist of a protein with one or more sugar chains attached to its
10 surface. The mammalian gene fucosyltransferase 8 (FUT8) encodes an enzyme called alpha-1,6-
11 fucosyltransferase, which is responsible for the transfer of a particular sugar residue, fucose, to a
12 specific position within complex sugar chains that are attached to many glycoproteins, including
13 but not limited to antibodies. The resulting fucosyl residue is often referred to as a “core fucose.”
14 Deletion of the FUT8 gene and the resulting lack of core fucosylation has been shown to affect
15 the biological activities of various mammalian proteins, potentially with beneficial results, as
16 described below.

17 17. Antibodies are a class of glycoproteins central to the operation of the immune
18 system. Antibodies bind to antigens, *i.e.*, substances in a body that the body considers foreign.
19 Antigens are molecules, usually proteins, on the surface of cells, viruses, fungi, bacteria, and
20 some non-living substances such as toxins, chemicals, and foreign particles. Any substance
21 capable of triggering an immune response is considered an antigen.

22 18. Each antibody consists of four chains of amino acids—two identical heavy chains
23 and two identical light chains—which are folded into a three-dimensional structure. Each of the
24 heavy and light chains consists of a constant region and a variable region. The variable region is
25 the portion of the antibody in its three dimensional structure that binds to the antigen, and each
26 variable region has three complementarity determining regions (CDRs) that interact closely with
27 the portion of the antigen that binds to the antibody, which is called the epitope. The constant
28 region of an antibody determines which of the five major classes, IgM, IgG, IgA, IgD, and IgE,

the antibody will be classified as. Immunoglobulin G (IgG) is the main type of antibody found in blood and extracellular fluid, allowing it to control infection of body tissues. If circulating antibodies come in contact with the target or antigen they were generated to fight, then the antibodies bind to the target. Depending on the antigen, the binding may impede the biological process causing the disease or may recruit specialized cells to destroy the foreign substance.

19. At the molecular level, antibodies are known to be shaped like the letter Y, with a reactive antigen binding site at the tip of each branch so that antibodies can attach to antigens on the basis of their molecular shape. The two tips of its “Y” are specific to each antigen, allowing different antibodies to bind to different foreign antigens. The basic structure of an antibody can be diagrammed as shown below:



20. Antibodies have also been used to develop treatments for various diseases. The mechanism of action of such therapeutic antibodies includes “antibody-dependent cell-mediated cytotoxicity” (ADCC), which is the killing of an antibody-coated target cell by a cytotoxic effector cell through a process that involves releasing the content of cytotoxic granules or by expression of cell death inducing molecules. ADCC is triggered through interaction of target bound antibodies with certain Fc receptors, which are glycoproteins present on the effector cell surface that bind the Fc region of immunoglobulins (Ig). Effector cells that mediate ADCC include natural killer (NK) cells, monocytes, macrophages, neutrophils, eosinophils and dendritic cells. ADCC involving human IgG1, the most used IgG subclass for therapeutic antibodies, is

1 highly dependent on the glycosylation profile of its Fc region. In particular, presence of the sugar
2 fucose at a specific position in the Fc region is well known to influence ADCC activity strongly.
3 Antibodies lacking this core fucosylation can be produced in mammalian cell lines lacking the
4 FUT8 gene and show a significantly enhanced ADCC and an increased therapeutic efficacy in
5 clinical patients.

6 **Plaintiffs' Patented Innovations**

7 21. Originally founded in 1949, KHK is a Japan-based global specialty pharmaceutical
8 company formed from the combination of Kyowa Hakko Kyogo and Kirin Pharma in 2008.
9 KHK aims to enhance human health and well-being worldwide through innovative drug
10 discovery and global commercialization, driven by state-of-the-art technologies focused on core
11 therapeutic areas of oncology, nephrology, immunology and allergy, and central nervous system.

12 22. Founded in 2003, BioWa—a KHK subsidiary—is a biotechnology company
13 committed to improving health through achievements in life science and technology. BioWa's
14 mission and focus is the out-licensing of its therapeutic antibody technologies.

15 23. In the mid-1980s, KHK began cutting-edge research in the field of antibody
16 therapies. In the course of this research, KHK scientists discovered that the presence of fucose,
17 one of the sugars found in the complex sugar chains in the Fc region of an antibody, greatly
18 affects ADCC activity, a critical factor in therapeutic mechanism of an antibody. They
19 discovered that reduction or elimination of fucose in the sugar chains dramatically enhances
20 ADCC activity of an antibody—as much as 100 times *in vitro* compared to fucosylated antibodies.

21 24. Soon thereafter, KHK scientists demonstrated that the mechanism behind the
22 enhanced ADCC of a fucose-free antibody was its increased affinity to FcγRIIIa (CD16), the
23 major Fc receptor for ADCC in humans. To take advantage of this finding, they strategically
24 knocked out the FUT8 gene responsible for the addition of fucose to sugar chains, creating FUT8-
25 knock-out CHO cells, created a new production method for fucose-free antibodies in CHO cells
26 and created fucose-free antibodies.

27 25. The inventions underlying the Patents-in-Suit form the basis of the Plaintiffs'
28 award-winning POTELLIGENT® Technology, which applies an “intelligent” approach to

1 creating more potent antibodies. Plaintiffs' proprietary FUT8 knockout CHO cell line produces
2 100% fucose-free antibodies that have markedly higher ADCC than their fucosylated counterparts.
3 POTELLIGENT® Technology, for which KHK employees received Japan Bioindustry
4 Association's Kei Arima Memorial Award in 2005 and the Okochi Memorial Technology Prize in
5 2016, has been recognized as the global standard technology to enhance ADCC in therapeutic
6 antibodies and has led to the development of antibodies that themselves have received
7 commendation from government and industry bodies. BioWa possesses an exclusive worldwide
8 license to POTELLIGENT® Technology.

9 26. Plaintiffs' patent portfolio for POTELLIGENT® Technology includes patents,
10 such as the Patents-in-Suit, directed to FUT8 knockout cells and corresponding cell lines for
11 making antibodies that have increased ADCC activity. As described above in Paragraphs 15 to
12 16, the FUT8 gene encodes an enzyme called alpha-1,6-fucosyltransferase that catalyzes the
13 transfer of fucose to the core of the complex sugar chains attached to the IgG antibody's Fc
14 region.

15 **Defendants' Infringing Conduct**

16 27. On information and belief, Aragen is a contract research organization that offers
17 cell line development, protein expression and purification, molecular biology, cell biology
18 immunology, and diverse *in vivo* services to the biotechnology and pharmaceutical industries. On
19 information and belief, one of its offerings includes a CHO-DG44 host cell lines platform for
20 secreted proteins and other molecules of interest.

21 28. On information and belief, Transposagen is privately-held biotechnology company
22 that offers cell engineering and gene editing technologies and services that address the research
23 needs of academic and drug discovery investigators. On information and belief, Transposagen's
24 services include stable cell line creation, gene knock-out services, and gene knock-in or editing
25 services.

26 29. On information and belief, *Genetic Engineering & Biotechnology News* published
27 in its June 1, 2014 issue an article titled "Next-Generation Genome Engineering," in which
28

1 Aragen and Transposagen personnel describe a “Fut8 knockout project.” A copy of this article is
 2 attached hereto as Exhibit 4. According to the authors of the article:

3 Using XTN™ TALENs, we were able to target Fut8, the alpha1,6-fucosyltransferase
 4 gene, thereby inactivating the fucosylation system and ***generating a genetically
 modified CHO cell line for producing afucosylated human therapeutics.*** Two
 5 rounds of transient transfection with expression plasmids encoding XTNs targeting
 6 exon 10 of Fut8, combined with a proprietary selection system for nonfucosylated
 7 cells, resulted in the generation of a pool of cells in which 80% of the cells ***lacked
 fucosylated cell-surface proteins,*** demonstrated by FACS analysis, and 78% of the
 Fut8 alleles had been inactivated. . . .

8 Importantly, ***antibodies expressed from these host cells were afucosylated and
 demonstrated the expected increased ADCC activity.*** Figure 2A demonstrates that
 9 antibody purified for multiple FUT8 knocked out subclones show only the G0 and G1
 peaks using a standard HPLC based assay.

10 Exhibit 4 (emphasis added).

11 30. On information and belief, on or around June 16, 2015, Aragen and Transposagen
 12 issued a joint press release announcing that they had developed a FUT8 knockout host cell line.
 13 A copy of this press release is attached hereto as Exhibit 5. The press release, titled “Aragen
 14 Bioscience, Inc. Partners with Transposagen Biopharmaceuticals, Inc. to Launch FUT8 Knockout
 15 CHO DG44 Cell Line Development Services,” stated:

16 Aragen Bioscience, Inc. (“Aragen Bioscience”), in partnership with Transposagen
 17 Biopharmaceuticals, Inc. (“Transposagen”), ***has developed a FUT8 knockout CHO
 DG44 host cell line.*** The elimination of the FUT8 gene results in afucosylated protein
 18 products. When applied to antibodies, the result is increased ADCC activity, and
 improved efficacy. Aragen Bioscience, is ***now offering protein expression and cell
 line development services with this cell line for products to be used for research
 19 purposes.*** The launch of a FUT8 knockout CHO DG44 host cell line for the
 20 development of high-expressing cell lines suitable for GMP manufacturing is expected
 in the second half of this year.

21 Transposagen is ***now offering custom gene editing services using the FUT8
 knockout CHO DG44 host cell line.*** Examples of custom services would be to
 22 rapidly and stably integrate a customer’s transgene into the cell line using the
 piggyBac™ DNA Modification System or to further genetically modify the cell line
 23 to enhance protein production. Transposagen ***will also offer gene editing kits
 containing the cell line*** and Transposagen’s unique technologies, including Footprint-
 24 Free™ Gene Editing, to create disease-specific cell lines and XTNT™ TALEN or
 NextGENTM CRISPRs to create additional gene knockouts and knock-ins. ***Industry
 25 and academic researchers will be able to create their own engineered cell lines or
 outsource the work,*** providing them with access to manufacturing services and a clear
 26 path to commercialization through partnerships with Transposagen and Aragen
 27 Bioscience.

28 Exhibit 5 (emphasis added).

1 31. On information and belief, Aragen and Transposagen's FUT8 knockout cell lines,
2 including at least the CHO DG44 host cell line, infringe one or more claims of the Patents-in-Suit.

3 32. By way of example, Claim 1 of the '232 Patent reads as follows:

4 An isolated mammalian host cell which has no α 1,6-fucosyltransferase activity for
5 adding fucose to N-acetylglucosamine of a reducing terminus of N-glycoside-linked
6 sugar chains by deleting a genomic gene encoding α 1,6-fucosyltransferase or by
7 adding a mutation to said genomic gene to eliminate the α 1,6-fucosyltransferase
activity, wherein said host cell is selected from the group consisting of a CHO cell, a
NSO cell, an SP2/0 cell, and a YB2/0 cell.

8 Claim 1 of the '232 Patent is directed to a mammalian host cell lacking α 1,6-fucosyltransferase
9 activity for adding fucose to N-acetylglucosamine of a reducing terminus of N-glycoside-linked
10 sugar chains by deleting a genomic gene encoding α 1,6-fucosyltransferase or by adding a
11 mutation to said genomic gene to eliminate the α 1,6-fucosyltransferase activity. Aragen and
12 Transposagen's FUT8 knockout CHO DG44 host cell lines are comprised of mammalian host
13 cells in which the FUT8 gene has been deleted. As a result of the FUT8 gene deletion, Aragen
14 and Transposagen's FUT8 knockout CHO DG44 host cell lines are comprised of mammalian host
15 cells that lack α 1,6-fucosyltransferase activity for adding fucose to N-acetylglucosamine of a
16 reducing terminus of N-glycoside-linked sugar chains. Claim 1 of the '232 Patent further recites
17 that the host cell is selected from the group consisting of a CHO cell, a NSO cell, an SP2/0 cell,
18 and a YB2/0 cell. Aragen's and Transposagen's FUT8 knockout CHO DG44 host cell lines are
19 comprised of CHO host cells. Accordingly, Aragen's and Transposagen's FUT8 knockout CHO
20 DG44 host cell lines satisfy each limitation of claim 1 of the '232 Patent.

21 33. As a further example, claim 1 of the '292 Patent reads as follows:

22 An isolated fucosyltransferase knock-out host cell wherein when a gene encoding an
23 antibody molecule is introduced in to said host cell, said host cell produces an
24 antibody composition comprising the antibody molecule, said host cell being a
mammalian cell, said antibody molecule comprising a Fc region comprising complex
25 N-glycoside-linked sugar chains bound to the Fc region, said sugar chains comprising
a reducing end which contains an N-acetylglucosamine, wherein the sugar chains do
26 not contain fucose bound to the 6 position of N-acetylglucosamine in the reducing end
of the sugar chains.

27 Claim 1 of the '292 Patent is directed to a mammalian fucosyltransferase knock-out host cell that
28 produces an antibody composition comprising the antibody molecule when a gene encoding an

antibody molecule is introduced in to said host cell. Upon introduction of a gene encoding an antibody into Aragen and Transposagen's FUT8 knockout CHO DG44 host cell line, the mammalian CHO DG44 host cells produce an antibody composition. Claim 1 further specifies that the antibody molecule comprises an Fc region comprising complex N-glycoside-linked sugar chains bound to the Fc region, the sugar chains comprising a reducing end which contains an N-acetylglucosamine. The antibody composition produced by Aragen and Transposagen's FUT8 knockout CHO DG44 host cell line when a gene encoding an antibody molecule is introduced into it comprises an antibody molecule with an Fc region comprising complex N-glycoside-linked sugar chains bound to the Fc region and the sugar chains comprise a reducing end which contains an N-acetylglucosamine. Claim 1 further specifies that the sugar chains on the antibody compositions do not contain fucose bound to the 6 position of N-acetylglucosamine in the reducing end of the sugar chains. Aragen and Transposagen's FUT8 knockout CHO DG44 host cell lines are comprised of fucosyltransferase knock-out host cells as a result of deleting the FUT8 gene, which encodes α 1,6-fucosyltransferase. As described in Paragraphs 15 to 17 above, the α 1,6-fucosyltransferase is responsible for the transfer of fucose to the core of the complex sugar chains attached to the IgG antibody's Fc region, specifically to the 6 position of N-acetylglucosamine in the reducing end. The sugar chains on the antibody compositions that result when a gene encoding an antibody molecule is introduced into Aragen and Transposagen's FUT8 knockout CHO DG44 host cell lines, therefore, do not contain fucose bound to the 6 position of N-acetylglucosamine in the reducing end of the sugar chains. Dependent claim 2 of the '292 Patent further recites that the host cell is a CHO cell. Aragen's and Transposagen's FUT8 knockout CHO DG44 host cell lines are comprised of individual CHO host cells. Accordingly, Aragen's and Transposagen's FUT8 knockout CHO DG44 host cell lines satisfy at least claims 1 and 2 of the '292 Patent.

34. As yet a further example, claim 1 of the '446 Patent reads as follows:

An isolated mammalian host cell which has decreased or no α 1,6-fucosyltransferase activity for adding fucose to N-acetylglucosamine of a reducing terminus of N-glycoside-linked sugar chains by deleting a gene encoding α 1,6-fucosyltransferase or by adding a mutation to said gene to reduce or eliminate the α 1,6-fucosyltransferase activity, wherein said mammalian host cell produces an antibody molecule.

1 Claim 1 of the '446 Patent is directed to a mammalian host cell that has decreased or no α 1,6-
2 fucosyltransferase activity due to a deletion of or mutation to the gene encoding α 1,6-
3 fucosyltransferase. Aragen and Transposagen's FUT8 knockout CHO DG44 host cell lines are
4 comprised of mammalian host cells that have no α 1,6-fucosyltransferase activity due to the
5 deletion of the FUT8 gene. As described in Paragraphs 15 to 17 above, the FUT8 gene encodes
6 α 1,6-fucosyltransferase. The mammalian host cell of claim 1 produces an antibody molecule. As
7 detailed in Paragraph 30 above, Aragen and Transposagen personnel describe a "Fut8 knockout
8 project" in which Aragen and Transposagen express antibodies from the FUT8 knockout CHO
9 DG44 host cell lines that were shown to be afucosylated and demonstrated the expected increased
10 ADCC activity. Dependent claim 2 of the '446 Patent further recites that the host cell is a CHO
11 cell. Aragen's and Transposagen's FUT8 knockout CHO DG44 host cell lines are comprised of
12 individual CHO host cells. Accordingly, Aragen and Transposagen's FUT8 knockout CHO
13 DG44 host cell lines satisfy claims 1 and 2 of the '446 Patent.

14 **Defendants' Knowledge of the Patents-in-Suit**

15 35. On December 17, 2015, KHK sent a letter to Aragen and Transposagen, stating
16 that it had come to KHK's attention that Aragen and Transposagen "may be making, using, and
17 selling FUT8 Knockout CHO DG44 host cell lines." KHK's letter further informed Aragen and
18 Transposagen that KHK is the owner of the '292 Patent, '446 Patent, and '232 Patent and asked
19 that Aragen and Transposagen "share with us your thoughts on whether your FUT8 Knockout
20 CHO DG44 host cell uses our patented technology." KHK's letter also provided Aragen and
21 Transposagen with claim language from exemplar claims of the '292 Patent, '446 Patent,
22 and '232 Patent, and compared that claim language to the description of Aragen and
23 Transposagen's activities relating to the FUT8 Knockout CHO DG44 host cell lines described in
24 their June 2015 press release.

25 36. On January 12, 2016, Transposagen, responded to KHK's December 17, 2015
26 letter. In that letter, Transposagen did not deny that it had made, used, sold, or offered to sell an
27 FUT8 Knockout CHO DG44 cell line.
28

1 FUT8 knockout cell lines capable of producing and/or that produce antibodies to conduct research,
2 including but not limited to research on the efficacy of the cell lines in producing afucosylated
3 human therapeutics.

4 44. Upon information and belief, and as a reasonable opportunity for further
5 investigation or discovery will show, Aragen and Transposagen also have directly infringed
6 and/or continue to infringe at least one claim of the '292 Patent by using in the United States
7 FUT8 knockout cell lines capable of producing and/or that produce antibodies to conduct testing,
8 including but not limited to testing of the efficacy of the cell lines in producing afucosylated
9 human therapeutics.

10 45. Upon information and belief, and as a reasonable opportunity for further
11 investigation or discovery will show, Aragen and Transposagen also have directly infringed
12 and/or continue to infringe at least one claim of the '292 Patent by using in the United States
13 FUT8 knockout cell lines capable of producing and/or that produce antibodies for marketing
14 purposes, including but not limited to demonstrating the efficacy of the cell lines in producing
15 afucosylated human therapeutics.

16 46. Upon information and belief, and as a reasonable opportunity for further
17 investigation or discovery will show, Aragen also has directly infringed and/or continues to
18 infringe at least one claim of the '292 Patent by using in the United States FUT8 knockout cell
19 lines capable of producing and/or that produce antibodies as part of protein expression and cell
20 line development services offered to and provided to customers and end users, including industry
21 and academic researchers.

22 47. Upon information and belief, and as a reasonable opportunity for further
23 investigation or discovery will show, Transposagen also has directly infringed and/or continues to
24 infringe at least one claim of the '292 Patent by using in the United States FUT8 knockout cell
25 lines capable of producing and/or that produce antibodies as part of custom gene editing services
26 offered to and provided to customers and end users, including industry and academic researchers.

27 48. Upon information and belief, and as a reasonable opportunity for further
28 investigation or discovery will show, Aragen and/or Transposagen also have directly infringed

1 and/or continue to infringe at least one claim of the '292 Patent by offering to sell, in the United
2 States, to customers and end users, including industry and academic researchers, FUT8 knockout
3 cell lines capable of producing and/or that produce antibodies.

4 49. Upon information and belief, and as a reasonable opportunity for further
5 investigation or discovery will show, Transposagen also has directly infringed and/or continues to
6 infringe at least one claim of the '292 Patent by offering to sell in the United States FUT8
7 knockout cell lines capable of producing and/or that produce antibodies to customers and end
8 users, including industry and academic researchers, as part of gene editing kits.

9 50. Upon information and belief, and as a reasonable opportunity for further
10 investigation or discovery will show, Transposagen also has directly infringed and/or continues to
11 infringe at least one claim of the '292 Patent by using in the United States FUT8 knockout cell
12 lines capable of producing and/or that produce antibodies as part of a screen for cells wherein the
13 FUT8 gene has been knocked out.

14 51. Upon information and belief, and as a reasonable opportunity for further
15 investigation or discovery will show, Transposagen also has directly infringed and/or continues to
16 infringe at least one claim of the '292 Patent by using in the United States FUT8 knockout cell
17 lines capable of producing and/or that produce antibodies for single cell cloning.

18 52. Upon information and belief, and as a reasonable opportunity for further
19 investigation or discovery will show, Transposagen also has directly infringed and/or continues to
20 infringe at least one claim of the '292 Patent by using in the United States FUT8 knockout cell
21 lines capable of producing and/or that produce antibodies for genotyping.

22 53. Upon information and belief, and as a reasonable opportunity for further
23 investigation or discovery will show, Transposagen also has directly infringed and/or continues to
24 infringe at least one claim of the '292 Patent by using in the United States FUT8 knockout cell
25 lines capable of producing and/or that produce antibodies for expanding the cell line and quality
26 control purposes.

27 54. Upon information and belief, and as a reasonable opportunity for further
28 investigation or discovery will show, Aragen also has directly infringed and/or continues to

1 infringe at least one claim of the '292 Patent by selling in the United States FUT8 knockout cell
2 lines capable of producing and/or that produce antibodies to customers and end users, including
3 industry and academic researchers.

4 55. A reasonable opportunity for further investigation or discovery will show that third
5 parties have directly infringed the '292 Patent by using in the United States FUT8 knockout cell
6 lines supplied by Aragen and/or Transposagen.

7 56. A reasonable opportunity for further investigation or discovery will show that third
8 parties have directly infringed the '292 Patent by making FUT8 knockout cell lines from FUT8
9 knockout cell lines supplied by Aragen and/or Transposagen in the United States.

10 57. A reasonable opportunity for further investigation or discovery will show that
11 Aragen and/or Transposagen have provided customers, end users, and/or each other with
12 materials for, instructions on, and assistance making and using FUT8 knockout cell lines, in the
13 United States.

14 58. A reasonable opportunity for further investigation or discovery will show that
15 Aragen and/or Transposagen have provided customers, end users, and/or each other with such
16 materials, instructions, and assistance with knowledge of the '292 Patent and a specific intent that
17 the FUT8 knockout cell lines will be made and/or will be used in a way that infringes at least one
18 claim of the '292 Patent.

19 59. On information and belief, and as a reasonable opportunity for further
20 investigation or discovery will show, the third parties to whom Aragen and/or Transposagen have
21 sold, provided, or otherwise supplied with FUT8 knockout cell lines have made in the United
22 States one or more FUT8 knockout cell lines that infringe at least one claim of the '292 Patent.

23 60. On information and belief, and as a reasonable opportunity for further
24 investigation or discovery will show, the third parties to whom Aragen and/or Transposagen have
25 sold, provided, or otherwise supplied with FUT8 knockout cell lines have used in the United
26 States one or more FUT8 knockout cell lines that infringe at least one claim of the '292 Patent.

27 61. A reasonable opportunity for further investigation or discovery will show that, in
28 violation of 35 U.S.C. § 271(b), Aragen and Transposagen have indirectly infringed and will

1 continue to indirectly infringe at least one claim of the '292 Patent by inducing direct
2 infringement of the '292 Patent by customers, end users, and/or each other.

3 62. A reasonable opportunity for further investigation or discovery will show that
4 FUT8 knockout cell lines are not a staple article or commodity of commerce suitable for any
5 substantial uses that do not infringe the '292 Patent.

6 63. A reasonable opportunity for further investigation or discovery will show that
7 Aragen and/or Transposagen have offered to sell and/or sold in the United States FUT8 knockout
8 cell lines, as described above, with knowledge that they are especially adapted for use in a
9 manner that infringes at least one claim of the '292 Patent.

10 64. A reasonable opportunity for further investigation or discovery will show that, in
11 violation of 35 U.S.C. § 271(c), Aragen and Transposagen have indirectly infringed and will
12 continue to indirectly infringe at least one claim of '292 Patent by contributing to direct
13 infringement of the '292 Patent by customers, end users, and/or each other.

14 65. On information and belief, Aragen and Transposagen will continue their
15 infringement of the '292 Patent unless enjoined by this Court.

16 66. Plaintiffs have suffered and will continue to suffer irreparable harm as a result of
17 Aragen and Transposagen's infringements of the '292 Patent.

18 67. Plaintiffs are entitled to all remedies at law and equity, including, but not limited
19 to, an injunction against Aragen and Transposagen's infringement of the '292 Patent pursuant to
20 35 U.S.C. § 283.

21 68. Plaintiffs have suffered and will continue to suffer monetary damages as a result of
22 Aragen and Transposagen's infringement of the '292 Patent.

23 69. On information and belief, Aragen and Transposagen's infringements of the '292
24 Patent have been with actual knowledge of the '292 Patent.

25 70. Based on this information and belief, Aragen and Transposagen's infringements of
26 the '292 Patent have been willful.

27 71. Plaintiffs are entitled to damages for Aragen and Transposagen's infringements of
28 the '292 Patent, including, but not limited to, damages pursuant to 35 U.S.C. §§ 284, 285.

SECOND CAUSE OF ACTION

(Infringement of the '446 Patent Against Defendants)

72. Plaintiffs reallege each and every allegation set forth in Paragraphs 1 through 71 and incorporate them here by reference.

73. A reasonable opportunity for further investigation or discovery will show that, in violation of 35 U.S.C. § 271(a), Aragen and Transposagen have infringed and continue to directly infringe at least one claim of the '446 Patent by making, using, offering for sale, selling, and/or importing in the United States FUT8 knockout cell lines that produce antibodies.

74. Specifically, upon information and belief, and as a reasonable opportunity for further investigation or discovery will show, Aragen and Transposagen directly infringed at least one claim of the '446 Patent by making in the United States one or more FUT8 knockout cell lines that produce antibodies.

75. Upon information and belief, and as a reasonable opportunity for further investigation or discovery will show, Aragen and Transposagen also have directly infringed and/or continue to infringe at least one claim of the '446 Patent by making in the United States FUT8 knockout cell lines that produce antibodies in connection with the infringing uses alleged below.

76. Upon information and belief, and as a reasonable opportunity for further investigation or discovery will show, Aragen and Transposagen also have directly infringed and/or continue to infringe at least one claim of the '446 Patent by using in the United States FUT8 knockout cell lines that produce antibodies to conduct research, including but not limited to research on the efficacy of the cell lines in producing afucosylated human therapeutics.

77. Upon information and belief, and as a reasonable opportunity for further investigation or discovery will show, Aragen and Transposagen also have directly infringed and/or continue to infringe at least one claim of the '446 Patent by using in the United States FUT8 knockout cell lines that produce antibodies to conduct testing, including but not limited to testing of the efficacy of the cell lines in producing afucosylated human therapeutics.

1 78. Upon information and belief, and as a reasonable opportunity for further
2 investigation or discovery will show, Aragen and Transposagen also have directly infringed
3 and/or continue to infringe at least one claim of the '446 Patent by using in the United States
4 FUT8 knockout cell lines that produce antibodies for marketing purposes, including but not
5 limited to demonstrating the efficacy of the cell lines in producing afucosylated human
6 therapeutics.

7 79. Upon information and belief, and as a reasonable opportunity for further
8 investigation or discovery will show, Aragen also has directly infringed and/or continues to
9 infringe at least one claim of the '446 Patent by using in the United States FUT8 knockout cell
10 lines that produce antibodies as part of protein expression and cell line development services
11 offered to and provided to customers and end users, including industry and academic researchers.

12 80. Upon information and belief, and as a reasonable opportunity for further
13 investigation or discovery will show, Aragen and/or Transposagen also have directly infringed
14 and/or continue to infringe at least one claim of the '446 Patent by offering to sell, in the United
15 States, to customers and end users, including industry and academic researchers, FUT8 knockout
16 cell lines that produce antibodies.

17 81. Upon information and belief, and as a reasonable opportunity for further
18 investigation or discovery will show, Transposagen also has directly infringed and/or continues to
19 infringe at least one claim of the '446 Patent by offering to sell in the United States FUT8
20 knockout cell lines that produce antibodies to customers and end users, including industry and
21 academic researchers, as part of gene editing kits.

22 82. Upon information and belief, and as a reasonable opportunity for further
23 investigation or discovery will show, Transposagen also has directly infringed and/or continues to
24 infringe at least one claim of the '446 Patent by using in the United States FUT8 knockout cell
25 lines that produce antibodies for single cell cloning.

26 83. Upon information and belief, and as a reasonable opportunity for further
27 investigation or discovery will show, Transposagen also has directly infringed and/or continues to
28

1 infringe at least one claim of the '446 Patent by using in the United States FUT8 knockout cell
2 lines that produce antibodies for genotyping.

3 84. Upon information and belief, and as a reasonable opportunity for further
4 investigation or discovery will show, Transposagen also has directly infringed and/or continues to
5 infringe at least one claim of the '446 Patent by using in the United States FUT8 knockout cell
6 lines that produce antibodies for expanding the cell line and quality control purposes.

7 85. Upon information and belief, and as a reasonable opportunity for further
8 investigation or discovery will show, Aragen also has directly infringed and/or continues to
9 infringe at least one claim of the '446 Patent by selling in the United States FUT8 knockout cell
10 lines that produce antibodies to customers and end users, including industry and academic
11 researchers.

12 86. A reasonable opportunity for further investigation or discovery will show that third
13 parties have directly infringed the '446 Patent by using in the United States FUT8 knockout cell
14 lines supplied by Aragen and/or Transposagen to produce antibodies.

15 87. A reasonable opportunity for further investigation or discovery will show that third
16 parties have directly infringed the '446 Patent by making FUT8 knockout cell lines from FUT8
17 knockout cell lines supplied by Aragen and/or Transposagen in the United States.

18 88. A reasonable opportunity for further investigation or discovery will show that
19 Aragen and/or Transposagen have provided customers, end users, and/or each other with
20 materials for, instructions on, and assistance making and using in the United States FUT8
21 knockout cell line to produce antibodies.

22 89. A reasonable opportunity for further investigation or discovery will show that
23 Aragen and/or Transposagen have provided customers, end users, and/or each other with such
24 materials, instructions, and assistance with knowledge of the '446 Patent and a specific intent that
25 FUT8 knockout cell lines that produce antibodies will be made and/or will be used in a way that
26 infringes at least one claim of the '446 Patent.

27 90. On information and belief, and as a reasonable opportunity for further
28 investigation or discovery will show, the third parties to whom Aragen and/or Transposagen have

1 sold, provided, or otherwise supplied with FUT8 knockout cell lines have made in the United
2 States one or more FUT8 knockout cell lines that produce antibodies.

3 91. On information and belief, and as a reasonable opportunity for further
4 investigation or discovery will show, the third parties to whom Aragen and/or Transposagen have
5 sold, provided, or otherwise supplied with FUT8 knockout cell lines have used in the United
6 States one or more FUT8 knockout cell lines that produce antibodies.

7 92. A reasonable opportunity for further investigation or discovery will show that, in
8 violation of 35 U.S.C. § 271(b), Aragen and Transposagen have indirectly infringed and will
9 continue to indirectly infringe at least one claim of the '446 Patent by inducing direct
10 infringement of the '446 Patent by customers, end users, and/or each other.

11 93. A reasonable opportunity for further investigation or discovery will show that
12 FUT8 knockout cell lines are not a staple article or commodity of commerce suitable for any
13 substantial uses that do not infringe the '446 Patent.

14 94. A reasonable opportunity for further investigation or discovery will show that
15 Aragen and/or Transposagen have offered to sell and/or sold in the United States FUT8 knockout
16 cell lines, as described above, with knowledge that they are especially adapted for use in a
17 manner that infringes at least one claim of the '446 Patent.

18 95. A reasonable opportunity for further investigation or discovery will show that, in
19 violation of 35 U.S.C. § 271(c), Aragen and Transposagen have indirectly infringed and will
20 continue to indirectly infringe at least one claim of '446 Patent by contributing to direct
21 infringement of the '446 Patent by customers, end users, and/or each other.

22 96. On information and belief, Aragen and Transposagen will continue their
23 infringement of the '446 Patent unless enjoined by this Court.

24 97. Plaintiffs have suffered and will continue to suffer irreparable harm as a result of
25 Aragen and Transposagen's infringements of the '446 Patent.

26 98. Plaintiffs are entitled to all remedies at law and equity, including, but not limited
27 to, an injunction against Aragen and Transposagen's infringement of the '446 Patent pursuant to
28 35 U.S.C. § 283.

1 99. Plaintiffs have suffered and will continue to suffer monetary damages as a result of
2 Aragen and Transposagen's infringement of the '446 Patent.

3 100. On information and belief, Aragen and Transposagen's infringements of the '446
4 Patent have been with actual knowledge of the '446 Patent.

5 101. Based on this information and belief, Aragen and Transposagen's infringements of
6 the '446 Patent have been willful.

7 102. Plaintiffs are entitled to damages for Aragen and Transposagen's infringements of
8 the '446 Patent, including, but not limited to, damages pursuant to 35 U.S.C. §§ 284, 285.

9 **THIRD CAUSE OF ACTION**

10 **(Infringement of the '232 Patent Against Defendants)**

11 103. Plaintiffs reallege each and every allegation set forth in Paragraphs 1 through 102
12 and incorporate them here by reference.

13 104. A reasonable opportunity for further investigation or discovery will show that, in
14 violation of 35 U.S.C. § 271(a), Aragen and Transposagen have infringed and continue to directly
15 infringe at least one claim of the '232 Patent by making, using, offering for sale, selling, and/or
16 importing in the United States FUT8 knockout cell lines.

17 105. Specifically, upon information and belief, and as a reasonable opportunity for
18 further investigation or discovery will show, Aragen and Transposagen directly infringed at least
19 one claim of the '232 Patent by making in the United States one or more FUT8 knockout cell
20 lines.

21 106. Upon information and belief, and as a reasonable opportunity for further
22 investigation or discovery will show, Aragen and Transposagen also have directly infringed
23 and/or continue to infringe at least one claim of the '232 Patent by making in the United States
24 FUT8 knockout cell lines prior to the introduction of an exogenous nucleic acid encoding an
25 antibody of interest into the cell line.

26 107. Upon information and belief, and as a reasonable opportunity for further
27 investigation or discovery will show, Aragen and Transposagen also have directly infringed
28

1 and/or continue to infringe at least one claim of the '232 Patent by making in the United States
2 FUT8 knockout cell lines in connection with the infringing uses alleged below.

3 108. Upon information and belief, and as a reasonable opportunity for further
4 investigation or discovery will show, Aragen and Transposagen also have directly infringed
5 and/or continue to infringe at least one claim of the '232 Patent by using in the United States
6 FUT8 knockout cell lines to conduct research, including but not limited to research on the
7 efficacy of the cell lines in producing afucosylated human therapeutics.

8 109. Upon information and belief, and as a reasonable opportunity for further
9 investigation or discovery will show, Aragen and Transposagen also have directly infringed
10 and/or continue to infringe at least one claim of the '232 Patent by using in the United States
11 FUT8 knockout cell lines to conduct testing, including but not limited to testing of the efficacy of
12 the cell lines in producing afucosylated human therapeutics.

13 110. Upon information and belief, and as a reasonable opportunity for further
14 investigation or discovery will show, Aragen and Transposagen also have directly infringed
15 and/or continue to infringe at least one claim of the '232 Patent by using in the United States
16 FUT8 knockout cell lines for marketing purposes, including but not limited to demonstrating the
17 efficacy of the cell lines in producing afucosylated human therapeutics.

18 111. Upon information and belief, and as a reasonable opportunity for further
19 investigation or discovery will show, Aragen also has directly infringed and/or continues to
20 infringe at least one claim of the '232 Patent by using in the United States FUT8 knockout cell
21 lines as part of protein expression and cell line development services offered to and provided to
22 customers and end users, including industry and academic researchers.

23 112. Upon information and belief, and as a reasonable opportunity for further
24 investigation or discovery will show, Transposagen also has directly infringed and/or continues to
25 infringe at least one claim of the '232 Patent by using in the United States FUT8 knockout cell
26 lines as part of custom gene editing services offered to and provided to customers and end users,
27 including industry and academic researchers.
28

1 113. Upon information and belief, and as a reasonable opportunity for further
2 investigation or discovery will show, Aragen and/or Transposagen also have directly infringed
3 and/or continue to infringe at least one claim of the '232 Patent by offering to sell, in the United
4 States, to customers and end users, including industry and academic researchers, FUT8 knockout
5 cell lines.

6 114. Upon information and belief, and as a reasonable opportunity for further
7 investigation or discovery will show, Transposagen also has directly infringed and/or continues to
8 infringe at least one claim of the '232 Patent by offering to sell in the United States FUT8
9 knockout cell lines to customers and end users, including industry and academic researchers, as
10 part of gene editing kits.

11 115. Upon information and belief, and as a reasonable opportunity for further
12 investigation or discovery will show, Transposagen also has directly infringed and/or continues to
13 infringe at least one claim of the '232 Patent by using in the United States FUT8 knockout cell
14 lines as part of a screen for cells wherein the FUT8 gene has been knocked out.

15 116. Upon information and belief, and as a reasonable opportunity for further
16 investigation or discovery will show, Transposagen also has directly infringed and/or continues to
17 infringe at least one claim of the '232 Patent by using in the United States FUT8 knockout cell
18 lines for single cell cloning.

19 117. Upon information and belief, and as a reasonable opportunity for further
20 investigation or discovery will show, Transposagen also has directly infringed and/or continues to
21 infringe at least one claim of the '232 Patent by using in the United States FUT8 knockout cell
22 lines for genotyping.

23 118. Upon information and belief, and as a reasonable opportunity for further
24 investigation or discovery will show, Transposagen also has directly infringed and/or continues to
25 infringe at least one claim of the '232 Patent by using in the United States FUT8 knockout cell
26 lines for expanding the cell line and quality control purposes.

27 119. Upon information and belief, and as a reasonable opportunity for further
28 investigation or discovery will show, Aragen also has directly infringed and/or continues to

1 infringe at least one claim of the '232 Patent by selling in the United States FUT8 knockout cell
2 lines to customers and end users, including industry and academic researchers.

3 120. A reasonable opportunity for further investigation or discovery will show that third
4 parties have directly infringed the '232 Patent by using in the United States FUT8 knockout cell
5 lines supplied by Aragen and/or Transposagen.

6 121. A reasonable opportunity for further investigation or discovery will show that third
7 parties have directly infringed the '232 Patent by making FUT8 knockout cell lines supplied by
8 Aragen and/or Transposagen in the United States.

9 122. A reasonable opportunity for further investigation or discovery will show that
10 Aragen and/or Transposagen have provided customers, end users, and/or each other with
11 materials for, instructions on, and assistance making and using FUT8 knockout cell line, in the
12 United States.

13 123. A reasonable opportunity for further investigation or discovery will show that
14 Aragen and/or Transposagen have provided customers, end users, and/or each other with such
15 materials, instructions, and assistance with knowledge of the '232 Patent and a specific intent that
16 the FUT8 knockout cell lines will be made and/or will be used in a way that infringes at least one
17 claim of the '232 Patent.

18 124. On information and belief, and as a reasonable opportunity for further
19 investigation or discovery will show, the third parties to whom Aragen and/or Transposagen have
20 sold, provided, or otherwise supplied with the FUT8 knockout cell lines have made in the United
21 States one or more FUT8 knockout cell lines that infringe at least one claim of the '232 Patent.

22 125. On information and belief, and as a reasonable opportunity for further
23 investigation or discovery will show, the third parties to whom Aragen and/or Transposagen have
24 sold, provided, or otherwise supplied with the accused FUT8 knockout cell lines have used in the
25 United States one or more FUT8 knockout cell lines that infringe at least one claim of the '232
26 Patent.

27 126. A reasonable opportunity for further investigation or discovery will show that, in
28 violation of 35 U.S.C. § 271(b), Aragen and Transposagen have indirectly infringed and will

1 continue to indirectly infringe at least one claim of the '232 Patent by inducing direct
2 infringement of the '232 Patent by customers, end users, and/or each other.

3 127. A reasonable opportunity for further investigation or discovery will show that
4 FUT8 knockout cell lines are not a staple article or commodity of commerce suitable for any
5 substantial uses that do not infringe the '232 Patent.

6 128. A reasonable opportunity for further investigation or discovery will show that
7 Aragen and/or Transposagen have offered to sell and/or sold in the United States FUT8 knockout
8 cell lines, as described above, with knowledge that it is especially adapted for use in a manner
9 that infringes at least one claim of the '232 Patent.

10 129. A reasonable opportunity for further investigation or discovery will show that, in
11 violation of 35 U.S.C. § 271(c), Aragen and Transposagen have indirectly infringed and will
12 continue to indirectly infringe at least one claim of '232 Patent by contributing to direct
13 infringement of the '232 Patent by customers, end users, and/or each other.

14 130. On information and belief, Aragen and Transposagen will continue their
15 infringement of the '232 Patent unless enjoined by this Court.

16 131. Plaintiffs have suffered and will continue to suffer irreparable harm as a result of
17 Aragen and Transposagen's infringements of the '232 Patent.

18 132. Plaintiffs are entitled to all remedies at law and equity, including, but not limited
19 to, an injunction against Aragen and Transposagen's infringement of the '232 Patent pursuant to
20 35 U.S.C. § 283.

21 133. Plaintiffs have suffered and will continue to suffer monetary damages as a result of
22 Aragen and Transposagen's infringement of the '232 Patent.

23 134. On information and belief, Aragen and Transposagen's infringements of the '232
24 Patent have been with actual knowledge of the '232 Patent.

25 135. Based on this information and belief, Aragen and Transposagen's infringements of
26 the '232 Patent have been willful.

27 136. Plaintiffs are entitled to damages for Aragen and Transposagen's infringements of
28 the '232 Patent, including, but not limited to, damages pursuant to 35 U.S.C. §§ 284, 285.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs KHK and BioWa pray that this Court:

A. Enter judgment in favor of Plaintiffs KHK and BioWa and against Defendants Aragen and Transposagen on all claims, counterclaims, and defenses at issue in this dispute, and hold that Aragen and Transposagen have directly and indirectly infringed the Patents-in-Suit;

B. Preliminarily and permanently enjoin Defendants Aragen and Transposagen and their respective officers, employees, agents, servants, attorneys, instrumentalities, and/or those in privity with them, from directly or indirectly engaging in acts that infringe the Patents-in-Suit;

C. Award Plaintiffs KHK and BioWa monetary damages adequate to compensate for Defendants Aragen and Transposagen's infringement of the Patents-in-Suit, together with pre-judgment and post-judgment interest on the damages so awarded;

D. Declare this case exceptional and award, up to and including, treble the amount of damages, together with fees, disbursements, and costs in accordance with 35 U.S.C. § 285; and

E. Award Plaintiffs KHK and BioWa all other just and proper relief.

Dated: October 17, 2016

Respectfully submitted,

JONES DAY

By: /s/ S. Christian Platt
S. Christian Platt

Counsel for Plaintiffs
KYOWA HAKKO KIRIN CO., LTD. AND
BIOWA, INC.

JURY TRIAL DEMAND

Pursuant to Rule 38(b) of the Federal Rules of Civil Procedure, Plaintiffs KHK and BioWa demand a trial by jury of all issues triable of right by jury.

Dated: October 17, 2016

Respectfully submitted,

JONES DAY

By: /s/ S. Christian Platt

S. Christian Platt

Counsel for Plaintiffs
KYOWA HAKKO KIRIN CO., LTD. AND
BIOWA, INC.