Anthony M. Insogna (State Bar No. 235792) (*N.D. Cal. Adm. Pending)*
aminsogna@jonesday.com
S. Christian Platt (State Bar No. 199318)
cplatt@jonesday.com
JONES DAY
San Diego Office
12265 El Camino Real, Suite 200
San Diego, CA 92130
Telephone: +1.858.314.1130
Facsimile: +1.858.314.1150

Jacqueline K. S. Lee (State Bar No. 247705)
jkslee@JonesDay.com
JONES DAY
Silicon Valley Office
1755 Embarcadero Road
Palo Alto, CA 94303
Telephone: +1.650.739.3939
Facsimile: +1.650.739.3900

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

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

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

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

JURISDICTION AND VENUE

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

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

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

8. Personal jurisdiction over Transposagen is proper because Transposagen has purposefully availed itself of the rights and privileges of conducting business in California, including but not limited to its publicized partnership with Aragen relating to the Defendants' 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,

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

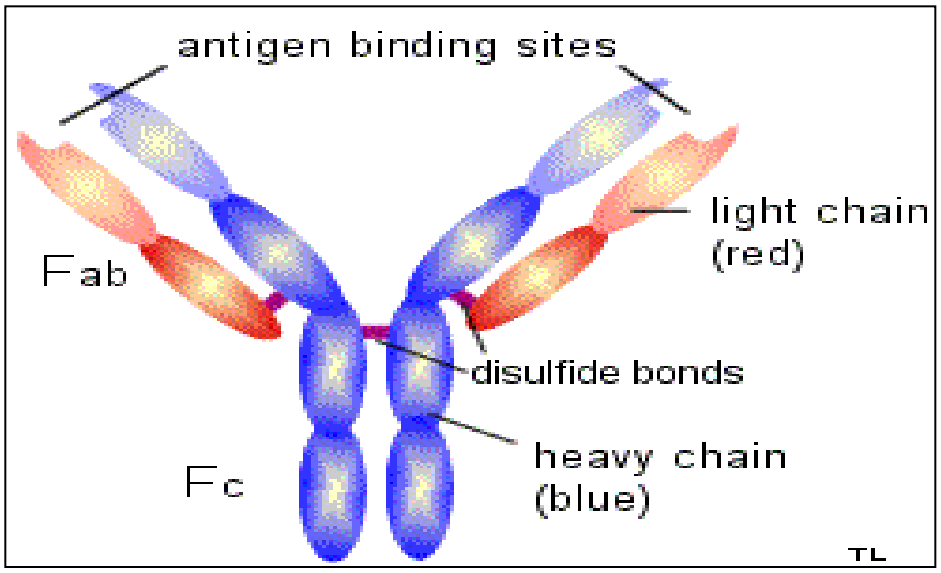
16. Among other things, CHO cell lines can be used to produce glycoproteins. Glycoproteins are molecules that consist of a protein with one or more sugar chains attached to its surface. The mammalian gene fucosyltransferase 8 (FUT8) encodes an enzyme called alpha-1,6-fucosyltransferase, which is responsible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

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

18. Each antibody consists of four chains of amino acids—two identical heavy chains and two identical light chains—which are folded into a three-dimensional structure. Each of the heavy and light chains consists of a constant region and a variable region. The variable region is the portion of the antibody in its three dimensional structure that binds to the antigen, and each variable region has three complementarity determining regions (CDRs) that interact closely with the portion of the antigen that binds to the antibody, which is called the epitope. The constant 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

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

Plaintiffs' Patented Innovations

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

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

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

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

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

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

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

Defendants' Infringing Conduct

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

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

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

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

> Using XTN™ TALENs, we were able to target Fut8, the alpha1,6-fucosyltransferase gene, thereby inactivating the fucosylation system and ***generating a genetically modified CHO cell line for producing afucosylated human therapeutics***. Two rounds of transient transfection with expression plasmids encoding XTNs targeting exon 10 of Fut8, combined with a proprietary selection system for nonfucosylated 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. . . .
>
> Importantly, ***antibodies expressed from these host cells were afucosylated and demonstrated the expected increased ADCC activity.*** Figure 2A demonstrates that antibody purifed for multiple FUT8 knocked out subclones show only the G0 and G1 peaks using a standard HPLC based assay.

Exhibit 4 (emphasis added).

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

> Aragen Bioscience, Inc. ("Aragen Bioscience"), in partnership with Transposagen Biopharmaceuticals, Inc. ("Transposagen"), ***has developed a FUT8 knockout CHO DG44 host cell line***. The elimination of the FUT8 gene results in afucosylated protein 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 purposes.*** The launch of a FUT8 knockout CHO DG44 host cell line for the development of high-expressing cell lines suitable for GMP manufacturing is expected in the second half of this year.
>
> Transposagen is ***now offering custom gene editing services using the FUT8 knockout CHO DG44 host cell line.*** Examples of custom services would be to rapidly and stably integrate a customer's transgene into the cell line using the piggyBacTM DNA Modification System or to further genetically modify the cell line to enhance protein production. Transposagen ***will also offer gene editing kits containing the cell line*** and Transposagen's unique technologies, including Footprint-FreeTM Gene Editing, to create disease-specific cell lines and XTNTM TALEN or NextGENTM CRISPRs to create additional gene knockouts and knock-ins. ***Industry 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 path to commercialization through partnerships with Transposagen and Aragen Bioscience.

Exhibit 5 (emphasis added).

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

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

> An isolated mammalian host cell which has no α1,6-fucosyltransferase activity for adding fucose to N-acetylglucosamine of a reducing terminus of N-glycoside-linked sugar chains by deleting a genomic gene encoding α1,6-fucosyltransferase or by adding a mutation to said genomic gene to eliminate the α1,6-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.

Claim 1 of the '232 Patent is directed to a mammalian host cell lacking α1,6-fucosyltransferase activity for adding fucose to N-acetylglucosamine of a reducing terminus of N-glycoside-linked sugar chains by deleting a genomic gene encoding α1,6-fucosyltransferase or by adding a mutation to said genomic gene to eliminate the α1,6-fucosyltransferase activity. Aragen and Transposagen's FUT8 knockout CHO DG44 host cell lines are comprised of mammalian host cells in which the FUT8 gene has been deleted. As a result of the FUT8 gene deletion, Aragen and Transposagen's FUT8 knockout CHO DG44 host cell lines are comprised of mammalian host cells that lack α1,6-fucosyltransferase activity for adding fucose to N-acetylglucosamine of a reducing terminus of N-glycoside-linked sugar chains. Claim 1 of the '232 Patent further recites that the host cell is selected from the group consisting of a CHO cell, a NSO cell, an SP2/0 cell, and a YB2/0 cell. Aragen's and Transposagen's FUT8 knockout CHO DG44 host cell lines are comprised of CHO host cells. Accordingly, Aragen's and Transposagen's FUT8 knockout CHO DG44 host cell lines satisfy each limitation of claim 1 of the '232 Patent.

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

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

Claim 1 of the '292 Patent is directed to a mammalian fucosyltransferase knock-out host cell that 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 α1,6-fucosyltransferase. As described in Paragraphs 15 to 17 above, the α1,6-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-fucosyltranferase activity, wherein said mammalian host cell produces an antibody molecule.

Claim 1 of the '446 Patent is directed to a mammalian host cell that has decreased or no α 1,6-fucosyltransferase activity due to a deletion of or mutation to the gene encoding α 1,6-fucosyltransferase. Aragen and Transposagen's FUT8 knockout CHO DG44 host cell lines are comprised of mammalian host cells that have no α1,6-fucosyltransferase activity due to the deletion of the FUT8 gene. As described in Paragraphs 15 to 17 above, the FUT8 gene encodes α1,6-fucosyltransferase. The mammalian host cell of claim 1 produces an antibody molecule. As detailed in Paragraph 30 above, Aragen and Transposagen personnel describe a "Fut8 knockout project" in which Aragen and Transposagen express antibodies from the FUT8 knockout CHO DG44 host cell lines that were shown to be afucosylated and demonstrated the expected increased ADCC activity. Dependent claim 2 of the '446 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 and Transposagen's FUT8 knockout CHO DG44 host cell lines satisfy claims 1 and 2 of the '446 Patent.

Defendants' Knowledge of the Patents-in-Suit

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

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

37. On January 14, 2016, Aragen, responded to KHK's December 17, 2015 letter. In its response, Aragen conceded that "Aragen is aware of the patents you have identified" and did not deny that it had made, used, sold, or offered to sell FUT8 knockout CHO DG44 cell lines that use KHK's patented inventions.

38. Although KHK and Aragen have engaged in further discussions regarding Aragen's infringement of the Patents-in-Suit, Aragen has never denied that it has made, used, sold, or offered to sell FUT8 knockout CHO DG44 cell lines that use the patented inventions claimed in the Patents-in-Suit.

FIRST CAUSE OF ACTION

(Infringement of the '292 Patent Against Defendants)

39. Plaintiffs reallege each and every allegation set forth in Paragraphs 1 through 38 and incorporate them here by reference.

40. 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 '292 Patent by making, using, offering for sale, selling, and/or importing in the United States FUT8 knockout cell lines capable of producing and/or that produce antibodies.

41. 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 '292 Patent by making in the United States one or more FUT8 knockout cell lines capable of producing and/or that produce antibodies.

42. 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 '292 Patent by making in the United States FUT8 knockout cell lines in connection with the infringing uses alleged below.

43. 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 '292 Patent by using in the United States

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

44. 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 '292 Patent by using in the United States FUT8 knockout cell lines capable of producing and/or that produce antibodies to conduct testing, including but not limited to testing of the efficacy of the cell lines in producing afucosylated human therapeutics.

45. 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 '292 Patent by using in the United States FUT8 knockout cell lines capable of producing and/or that produce antibodies for marketing purposes, including but not limited to demonstrating the efficacy of the cell lines in producing afucosylated human therapeutics.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

71. Plaintiffs are entitled to damages for Aragen and Transposagen's infringements of 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.

78. 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 for marketing purposes, including but not limited to demonstrating the efficacy of the cell lines in producing afucosylated human therapeutics.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

THIRD CAUSE OF ACTION

(Infringement of the '232 Patent Against Defendants)

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

104. 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 '232 Patent by making, using, offering for sale, selling, and/or importing in the United States FUT8 knockout cell lines.

105. 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 '232 Patent by making in the United States one or more FUT8 knockout cell lines.

106. 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 '232 Patent by making in the United States FUT8 knockout cell lines prior to the introduction of an exogenous nucleic acid encoding an antibody of interest into the cell line.

107. 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 '232 Patent by making in the United States FUT8 knockout cell lines in connection with the infringing uses alleged below.

108. 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 '232 Patent by using in the United States FUT8 knockout cell lines to conduct research, including but not limited to research on the efficacy of the cell lines in producing afucosylated human therapeutics.

109. 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 '232 Patent by using in the United States FUT8 knockout cell lines to conduct testing, including but not limited to testing of the efficacy of the cell lines in producing afucosylated human therapeutics.

110. 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 '232 Patent by using in the United States FUT8 knockout cell lines for marketing purposes, including but not limited to demonstrating the efficacy of the cell lines in producing afucosylated human therapeutics.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

136. Plaintiffs are entitled to damages for Aragen and Transposagen’s infringements of 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.