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January 8, 2020

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By USDA APHIS BRS Document Control Officer at 3:20 pm, Jan 10, 2020

Bernadette Juarez
APHIS Deputy Administrator
Biotechnology Regulatory Services
4700 River Rd, Unit 98
Riverdale, MD 20737

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Re: Confirmation of Regulatory Status of Multiplex Genome-Edited Camelina Null Segregant Lines Developed by CRISPR/Cas Technology

Dear Ms. Juarez,

Yield10 Bioscience respectfully requests confirmation from USDA-APHIS's Biotechnology Regulatory Services (BRS) that our genome-edited *Camelina sativa* (L.) Crantz plant lines developed using the CRISPR/Cas9 genome editing technology do not meet the definition of regulated articles under 7 CFR Part 340 since the final lines do not contain any DNA from a "plant pest". *Camelina sativa* is an oil seed crop in the family Brassicaceae that is not on the USDA federal noxious weed list. The lines, herein referred to as lines [CBI-Deleted], were developed at Metabolix Oilseeds, Inc. (110 Gymnasium Place, Saskatoon, SK, S7N 0W9, Canada), a wholly owned Canadian subsidiary of Yield10 Bioscience. We used disarmed *Agrobacterium tumefaciens* to deliver a gene encoding the endonuclease Cas9, as well as three cassettes coding each for a different guide RNA to direct the Cas9 enzyme to defined sites in the plant genome, into plant cells. The targeted sites for genome editing were [CBI-Deleted] genes present in Camelina, [2x CBI-Deleted] that [CBI-Deleted]. The inactivation of the [3x CBI-Deleted] genes is thus expected to [CBI-Deleted].

It has been shown previously by other researchers that the Cas9 enzyme produces double strand DNA breaks that when repaired, incorporate small deletions or insertions of DNA. DNA sequence analysis has shown that lines [CBI-Deleted] contain two to twenty-two nucleotide deletions that either disrupt the coding sequence of the [CBI-Deleted] genes, or that delete one codon from the genes. [CBI-Deleted]. Please see Table 1 for a summary of the nature of edits on [CBI-Deleted] genes.

As described below, lines [CBI-Deleted] are null segregants that were obtained using conventional breeding procedures to

remove the genetic sequences that allow the CRISPR/Cas9 editing to take place such that only the genome edits (two to twenty-two nucleotide deletions) remain. Analysis of the bulk parent [ ] seed of the lines shows that they produce [ ]. **2x CBI-Deleted**
In parent line of lines [ ] edited [**2x CBI-Deleted**
]. In the parent line of [ ] the [**3x CBI-Deleted**
] as well which leads to [ ]. **2x CBI-Deleted**

In parent plants of lines [ ] edited in only the [ ] gene, the **2x CBI-Deleted**
[ ]. Together with [**2x CBI-Deleted**
], this leads to [**2x CBI-Deleted**
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In parent plants of [ ] that are edited in [**2x CBI-Deleted**
], the [ ]. **2x CBI-Deleted**
Together with [ ], this leads to [**2x CBI-Deleted**
]. **CBI-Deleted**

Since lines [ ] **CBI-Deleted**
are null segregants that do not contain any plant pest sequences, and since the two to twenty-two nucleotide deletions do not generate a plant pest or pose increased weediness potential, it is our opinion that lines [**CBI-Deleted**
] do not meet the definition of a regulated article based on 7 CFR Part 340. We however **CBI-Deleted**
seek confirmation of the regulatory status of lines [**CBI-Deleted**
] from USDA-APHIS BRS. **CBI-Deleted**

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]

Table 1. Summary of nucleotide deletions in genes [ ] in edited Camelina lines. Abbreviations are as follows: WT, wild type (no change in nucleotide sequence); Ch, chromosome. Numbers in table designate the size of the deletion in the targeted gene.

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Intended Phenotype

The intended phenotype of lines produced from editing of the [ ] via inactivation of the endogenous [ ] genes that [ ]. Camelina is an allohexaploid and contains three subgenomes such that there are three copies, or homeologs, of each gene in the plant. Thus complete editing of the [ ] genes in a plant would contain edits in nine genes. Since homozygous or biallelic edits are needed for stable lines, 18 total editing targets would be edited in a completely edited plant. As depicted in detail in Table 1, we generated two lines [ ] that are [ ], such that [ ] gene targets are edited. [ ] lines [ ] bear edits [ ]. [ ] line [ ], bears edits [ ]. Finally, lines [ ] show editing in [ ].

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Intended Activity

Upon confirmation from USDA-APHIS BRS that the [ ] edited Camelina lines are not regulated, Yield10 Bioscience intends to import the lines from its subsidiary in Saskatoon, Canada. In addition, we plan to conduct field releases and interstate movement of the lines.

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Genetic Change in the Final Product

The genetic changes are deletions of [ ], in copies of the [*]* genes. The best edited lines, [ ], have homozygous edits in [ ] in total. These edits are indistinguishable from changes that could result from native genome variability, conventional breeding, or chemical or radiation-based mutagenesis.

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Development of the Edited Camelina Lines

The components for the CRISPR/Cas9 genome editing technology, namely an expression cassette for the gene encoding the Cas9 endonuclease and three expression cassettes for three guide RNAs to target the Cas9 to the desired sites in the Camelina genome, were delivered into the plant cells by *Agrobacterium*-mediated transformation using a binary vector and the floral dip method. CRISPR/Cas9 is a bacterial endonuclease. It utilizes a combination of protein-DNA and RNA-DNA pairing to direct targeted double strand breaks in the DNA sequence of interest. The guide RNA targets Cas9 to the intended site of action. The spacers of the guide RNAs ([ ] CsC1-69, [ ] CsC2-33, and [ ] CsC3-52) were designed to provide sufficient guide RNA specificity (Table 2), to generate an edit in all three gene copies (6 editing targets for biallelic edits) of each gene's respective target gene. A detailed list of genetic elements, their origin, and their function is presented in Table 2. In short, the T-DNA of binary vector [ ] carries five expression cassettes:

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- An expression cassette for the two exons of Cas9 endonuclease from *Streptococcus pyogenes* [**CBI-Deleted**
  ]. The expression of the Cas9 gene is controlled by the [**2x CBI-Deleted** **CBI-Deleted** **CBI-Deleted** **CBI-Deleted**
  ].
- A cassette encoding the guide RNA [ ] spacer CsC1-69 under control of the polymerase III promoter of the U6-26 small nuclear RNA gene from [ ] **CBI-Deleted** **CBI-Deleted**
- A cassette encoding the guide RNA [ ] spacer CsC2-33 under control of the polymerase III promoter of the U6-26 small nuclear RNA gene from [ ] **CBI-Deleted** **CBI-Deleted**
- A cassette encoding the guide RNA [ ] spacer CsC3-52 under control of the polymerase III promoter of the U6-26 small nuclear RNA gene from [ ] **CBI-Deleted** **CBI-Deleted**
- An expression cassette for the [ ] selection marker **CBI-Deleted**

Table 2. Genetic Elements of [ ] used to create lines [ ]. The vector backbone (region outside of the T-DNA) is identical to standard binary vector [ ]. **2x CBI-Deleted** **CBI-Deleted** **CBI-Deleted**

	Genetic Element	Source	Function	
Cassette 1	U6-26 promoter	*[ ]*	Polymerase III promoter of the U6-26 small nuclear RNA gene to drive transcription of cassette 1 composed of the [ ] CsC3-52 spacer and the guide RNA scaffold which together encode the functional chimeric guide RNA	**CBI-Deleted** **CBI-Deleted** **CBI-Deleted**
	[ ] CsC3-52 spacer	*Camelina sativa*	Encodes [ ]. This "spacer" directs the Cas9 endonuclease to the [ ] genes for cleavage	**2x CBI-Deleted** **CBI-Deleted** **CBI-Deleted** **CBI-Deleted**
	Guide RNA scaffold	*Streptococcus pyogenes*	Encodes crRNA-tracrRNA fusion transcript that is necessary for Cas9 binding. The [ ] CsC3-52 spacer and the guide RNA scaffold together constitute a functional chimeric guide RNA	**CBI-Deleted**
	U6-26 terminator	*[ ]*	Terminator of U6-26 small nuclear RNA polymerase III to terminate transcription of [ ] CsC3-52 spacer and guide RNA scaffold	**CBI-Deleted** **2x CBI-Deleted**

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Cassette 2	U6-26 promoter	*[ ]*	Polymerase III promoter of the U6-26 small nuclear RNA gene to drive transcription of cassette 2 composed of the [ ] CsC1-69 spacer and the guide RNA scaffold which together encode the functional chimeric guide RNA	**CBI-Deleted** **CBI-Deleted** **CBI-Deleted**
	[ ] CsC1-69	*Camelina sativa*	Encodes [ ]. This "spacer" directs the Cas9 endonuclease to the [ ] genes for cleavage	**2x CBI-Deleted** **CBI-Deleted** **CBI-Deleted** **CBI-Deleted**
	Guide RNA scaffold	*Streptococcus pyogenes*	Encodes crRNA-tracrRNA fusion transcript that is necessary for Cas9 binding. The [ ] CsC1-69 spacer and the guide RNA scaffold together constitute a functional chimeric guide RNA	**CBI-Deleted**
	U6-26 terminator	*[ ]*	Terminator of U6-26 small nuclear RNA polymerase III to terminate transcription of [ ] CsC1-69 spacer and guide RNA scaffold	**CBI-Deleted** **2x CBI-Deleted**
Cassette 3	U6-26 promoter	*[ ]*	Polymerase III promoter of the U6-26 small nuclear RNA gene to drive transcription of cassette 3 composed of the [ ] CsC2-33 spacer and the guide RNA scaffold which together encode the functional chimeric guide RNA	**CBI-Deleted** **CBI-Deleted** **CBI-Deleted**
	[ ] CsC2-33 spacer	*Camelina sativa*	Encodes [ ]. This "spacer" directs the Cas9 endonuclease to the [ ] genes for cleavage	**2x CBI-Deleted** **CBI-Deleted** **CBI-Deleted** **CBI-Deleted**
	Guide RNA scaffold	*Streptococcus pyogenes*	Encodes crRNA-tracrRNA fusion transcript that is necessary for Cas9 binding. The [ ] CsC2-33 spacer and the guide RNA scaffold together constitute a functional chimeric guide RNA	**CBI-Deleted**
	U6-26 terminator	*[ ]*	Terminator of U6-26 small nuclear RNA polymerase III to terminate transcription of [ ] CsC2-33 spacer and guide RNA scaffold	**CBI-Deleted** **2x CBI-Deleted**
Cassette 4	[ ] promoter	*[ ]*	[ ], controls expression of the Cas9 coding sequence	**3x CBI-Deleted** **2x CBI-Deleted** **2x CBI-Deleted** **CBI-Deleted**
	[ ]	[ ]	[ ]	**3x CBI-Deleted** **CBI-Deleted**
	[ ]	[ ]	[ ]	**3x CBI-Deleted** **2x CBI-Deleted**
	[ ]	*Streptococcus pyogenes*	Exon 1 of Cas9 endonuclease [ ]	**2x CBI-Deleted** **CBI-Deleted**
	[ ]	*Solanum tuberosum*	[ ] to optimize Cas9 expression in plants	**2x CBI-Deleted** **CBI-Deleted**
	[ ]	*Streptococcus pyogenes*	Exon 2 of Cas9 endonuclease [ ]	**2x CBI-Deleted** **CBI-Deleted**
	[ ]	*[ ]*	[	**3x CBI-Deleted** **CBI-Deleted**

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			]	**CBI-Deleted** **CBI-Deleted**
	[ ] terminator	*[ ]*	Terminator of the [ ] to terminate transcription of Cas9	**3x CBI-Deleted** **CBI-Deleted**
Cassette 5	[ ] promoter	[ ]	[ ] promoter, drives expression of the [ ] selection marker	**3x CBI-Deleted** **2x CBI-Deleted**
	[ ] selection marker	*[ ]*	[ ]	**3x CBI-Deleted** **2x CBI-Deleted** **CBI-Deleted** **CBI-Deleted** **CBI-Deleted** **CBI-Deleted** **CBI-Deleted**
	[ ] terminator	[ ]	Terminator of the [ ] gene to terminate transcription of the [ ] selection marker	**3x CBI-Deleted** **2x CBI-Deleted**
	T-DNA Left Border	*Agrobacterium tumefaciens* Ti plasmid	Left border of the T-DNA, required for transfer of the T-DNA into the plant cell genome	
	aphAIII	*Escherichia coli K-12*	Bacterial kanamycin resistance marker, provides kanamycin resistance for plasmid maintenance in *E. coli*	
	pBR322 ori	*Escherichia coli K-12*	Bacterial origin of replication from plasmid pMB1, used for plasmid maintenance in *E. coli*	
	pVS1 rep	*Pseudomonas aeruginosa* pVS1	Replication protein from plasmid pVS1, used for plasmid replication in *Agrobacterium*	
	pVS1 sta	*Pseudomonas aeruginosa* pVS1	Stability protein from plasmid pVS1, used for plasmid stability in *Agrobacterium*	
	T-DNA Right Border	*Agrobacterium tumefaciens* Ti plasmid	Right border of the T-DNA, required for transfer of the T-DNA into the plant cell genome	

The binary vector backbone is identical to the standard binary vector [ ] and includes both T-DNA borders. **CBI-Deleted** **CBI-Deleted**

The next step comprised [ ], indicating the presence of the T-DNA containing the Cas9 expression and guide RNA expression cassettes. T_1 generation seeds were planted in soil and leaf tissue was screened for genome editing by Amplicon sequencing. Plants containing genome edits in the [ ] loci were isolated. T_1 plants were grown and second-generation seed was isolated and screened for [ ]. The [ ] second generation seeds were further advanced through two additional generations to generate generation four and generation five seeds [ ]. **CBI-Deleted** **CBI-Deleted** **CBI-Deleted** **2x CBI-Deleted** **CBI-Deleted**

Additional analysis of the null segregant plant lines included Amplicon sequencing of all nine genes (18 biallelic editing targets) for [ ] to determine the nature of the editing. A summary of lines is shown below with more specific details in Table 1. **CBI-Deleted**

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a) Lines [ ] **CBI-Deleted**

- carry a [ ]. **CBI-Deleted** **CBI-Deleted**
- The remaining [ ] as well as [ ]. **2x CBI-Deleted** **CBI-Deleted**

b) Lines [ ] **CBI-Deleted**

- carry a [ ]. **CBI-Deleted** **CBI-Deleted**
- The remaining [ ] as well as [ ]. **2x CBI-Deleted** **CBI-Deleted**

c) Line [ ] **CBI-Deleted**

- carries a [ ]. **CBI-Deleted** **CBI-Deleted** **CBI-Deleted**
- The remaining [ ] as well as [ ]. **2x CBI-Deleted** **CBI-Deleted**

d) Lines [ ] **CBI-Deleted**

- carry a [ ] and a [ ]. **CBI-Deleted** **2x CBI-Deleted** **CBI-Deleted** **CBI-Deleted**
- The remaining [ ], [ ] as well as [ ]. **3x CBI-Deleted** **CBI-Deleted**

e) Lines [ ] **CBI-Deleted**

- carry a [ ]. **CBI-Deleted** **CBI-Deleted**
- The [ ] as well as [ ]. **2x CBI-Deleted** **CBI-Deleted**

Detailed PCR analysis was also performed using 16 primer pairs targeting multiple regions of the T-DNA insert, the vector backbone, as well as a couple of endogenous Camelina wild type control genes. No evidence of any T-DNA or plant vector backbone was detected in lines [ ]. Please find supporting data at the end of this document. **CBI-Deleted** **CBI-Deleted**

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Former USDA-APHIS Jurisdiction on CRISPR/Cas9 Genome Editing

In its responses to previous letters (listed below) USDA-APHIS has concluded that there is no reason to believe that targeted mutations generated by the gene editing process of Cas9 endonucleases would generate plant pests.

Reference	Date	Species
Firko to Dupont Pioneer	January 12, 2018	*Zea mays* - corn
Firko to USDA ARS	October 16, 2017	*Glycine max* - soybean
Firko to Yield10 Bioscience	August 29, 2017	*Camelina sativa*
Firko to Danforth Center	April 7, 2017	*Setaria viridis*
Firko to DuPont Pioneer	April 18, 2016	*Zea mays* - corn
Firko to Penn State University	April 13, 2016	*Agaricus bisporus* – white button mushroom

No Plant Pest Sequences Remain in the Edited Camelina Line

The edited Camelina lines were generated through expression of the Cas9 cassette. The [ ], pVS1, T-DNA borders and [ ] terminator are derived from plant pest sequences ([ ], *Pseudomonas aeruginosa*, [ ]) (Table 2) as designated in 7 CFR 340.2. However, these sequences are not involved in pathogenicity and do not express proteins that would result in infection or pathogenicity of the edited Camelina line. Importantly, the final edited Camelina lines [ ], are null segregants and do not contain these plant pest sequences but retain the desired edits.

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USDA-APHIS has previously made the determination that genetically modified plants transformed with Cas9 via *Agrobacterium*-mediated transformation are not regulated articles if it was experimentally shown that the Cas9-bearing T-DNA was segregated away from the targeted mutation through conventional breeding and produced progeny without the inserted DNA (see USDA response letters below).

Reference	Date	Species
Firko to University of Minnesota	June 17, 2019	*Glycine max* - soybean
Firko to University of Minnesota	June 17, 2019	*Glycine max* - soybean
Firko to Illinois State University	April 19, 2019	*Thlaspi arvense* L. - pennycress
Firko to Max Planck Institute	February 25, 2019	*Nicotiana attenuata* – coyote tobacco
Firko to Intrexon Corporation	February 8, 2019	*Lactuca sativa* -lettuce

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Firko to Yield10 Bioscience	September 7, 2018	*Camelina sativa*
Firko to Illinois State University	August 6, 2018	*Thlaspi arvense* L. - pennycress
Firko to Iowa State University	July 12, 2018	*Zea mays* -maize
Firko to University of Florida	May 14, 2018	*Solanum lycopersicum* - tomato
Firko to USDA ARS	October 16, 2017	*Glycine max* - soybean
Firko to Yield10 Bioscience	August 29, 2017	*Camelina sativa*
Firko to Danforth Center	April 7, 2017	*Setaria viridis*

In addition, USDA-APHIS has previously determined that other null segregants originally generated via *Agrobacterium*-mediated transformation are not regulated articles:

Reference	**Date**	**Species**
Firko to North Carolina State University	December 29, 2017	*Nicotiana tabacum* - tobacco
Firko to Epicrop technologies	April 7, 2017	*Glycine max* - soybean
Firko to Iowa State University	May 22, 2015	*Oryza sativa* – rice
Gregoire to University of Nebraska	June 6, 2012	*Sorghum bicolor*

The parent lines of lines [**CBI-Deleted**
] of our current inquiry were developed using a similar method as described in our **CBI-Deleted**
former letter of inquiry for the development of the genome-edited Camelina null segregant line [**CBI-Deleted**
] from June 12, 2017, as well as described in our former letter of inquiry for the development of **CBI-Deleted**
the null segregants of genome-edited lines containing multiple edits [**CBI-Deleted**
] from May 22, 2018 . In Dr. Firko's response letters dated **CBI-Deleted**
August 29, 2017 and September 7, 2018, USDA APHIS considered these lines not regulated pursuant to 7 CFR part 340.

USDA-APHIS has previously determined that plants edited in two or more genes are not regulated articles if it was experimentally shown that the genetic material used to create the edits was removed by segregation:

Reference	**Date**	**Species**
Firko to Illinois State University	April 19, 2019	*Thlaspi arvense* L. - pennycress
Firko to Max Planck Institute	February 25, 2019	*Nicotiana attenuata* – coyote tobacco
Firko to Yield10 Bioscience	September 7, 2018	*Camelina sativa*
Firko to USDA-ARS	October 16, 2017	*Glycine max* - soybean
Firko to Iowa State University	May 22, 2015	*Oryza sativa* - rice

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Conclusions

Metabolix Oilseeds, a wholly owned Canadian subsidiary of Yield10 Bioscience, generated [ ] CBI-Deleted
CRISPR/Cas9 edited lines of the allohexaploid species *Camelina sativa*. The lines, lines [ ] CBI-Deleted
], contain [ ] 2x CBI-Deleted
], in the [ ] genes. All [ ] lines [ ] 4x CBI-Deleted
] are null segregants (genes] CBI-Deleted
enabling CRISPR/Cas9 editing were removed through conventional breeding) yet retain the desired genome edits. Lines [ ] CBI-Deleted
] do not contain any foreign DNA or plant pest sequences.] CBI-Deleted

In order to facilitate further testing at our Woburn, MA facilities and in the field, Yield10 Biosciences requests confirmation from Biotechnology Regulatory Services that our edited Camelina lines [ ] CBI-Deleted
] do not meet] CBI-Deleted
the definition of a regulated article under 7 CFR Part 340.

We look forward to answering any questions you might have.

Sincerely,

Karen Bohmert-Tatarev, PhD
Senior Director, Rice
19 Presidential Way
Woburn, MA 01801
617-583-1769
kbohmert-tatarev@yield10bio.com

Kristi D. Snell, PhD
VP of Research & CSO
19 Presidential Way
Woburn, MA 01801
617-583-1729
snell@yield10bio.com

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Supporting Data

1. Map of transformation vector showing primer binding sites.

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2. **Description of primers used for screening of null segregants and expected amplicons**

Gel lane	**Primer 1** *(bases where primer binds in vector [ ])*	**Primer 2** *(bases where primer binds in vector [ ])*	**Genetic Fragments in Expected Amplicon**	**Expected Amplicon Size (bp)**
[				
				]

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3. Agarose gel electrophoresis analysis of PCR reactions of plant genomic DNA from lines [19-4925, 19-4931, 19-4935, 19-4938, 19-4973, 19-4997, 19-5000, 19-5007 and 19-5008] to demonstrate absence of transformation vector sequence in null segregants. PCR was performed with Top Taq Master Mix kit (Qiagen, Cat No./ID: 200403) with 5 µL reaction loaded on a 1.0% agarose gel. PCR cycling parameters for amplification of primer sets #4, #9, #10, #11, #12, #15 were one cycle at 95˚C for 5 min, 35 cycles at 95 ˚C for 30 sec, 64˚C for 30 s, 72 ˚C for 45 s followed by a final extension at 72˚C of 10 min. For all other primers the annealing temperature was 60˚C with other cycling conditions as described above. **CBI-Deleted** **CBI-Deleted**

a. [ ] control plasmid DNA **CBI-Deleted**

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b. [ ], wild-type control genomic DNA CBI-Deleted

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] CBI-Deleted

c. Water control (no DNA template)

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d. Line [19-4925] genomic DNA CBI-Deleted

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] CBI-Deleted

e. Line [ ] genomic DNA **CBI-Deleted**
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] **CBI-Deleted**

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f. Line [ ] genomic DNA CBI-Deleted
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g. Line [ ] genomic DNA **CBI-Deleted**
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h. Line [ ] genomic DNA **CBI-Deleted**

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i. Line [ ] genomic DNA **CBI-Deleted**

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j. Line [ ] genomic DNA CBI-Deleted
[CBI-Deleted

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k. Line [ ] genomic DNA CBI-Deleted

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I. Line [ ] genomic DNA **CBI-Deleted**

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