~~**WHAT IS CLAIMED IS:**~~

CLAIMS

1. A method of reducing bioburden of a chromatography resin comprising:

exposing a container comprising a composition comprising (i) a chromatography resin and (~~i~~ii) a liquid comprising benzyl alcohol and at least ~~one alcohol~~two antioxidant agents, to a dose of gamma-irradiation sufficient to reduce the bioburden of the container and the chromatography resin, wherein the ~~at least one alcohol is present in an amount~~concentration of benzyl alcohol in the liquid is 0.01% v/v to 10% v/v, and wherein benzyl alcohol and the at least two antioxidant agents are present in amounts sufficient to ameliorate the loss of binding capacity of the chromatography resin after exposure to the dose of gamma-irradiation.

2. The method of claim 1, wherein the container is a storage vessel.

3. The method of claim 1, wherein the container is a chromatography column.

4. The method of claim 1, wherein the container is a packed chromatography column.

5. The method of claim 1, wherein the composition is a slurry of sedimented chromatography resin.

6. The method of claim 1, wherein the at least ~~one alcohol is selected from the group of: benzyl alcohol, cyclohexanol, isobutyl alcohol, 2-methyl-2-butanol, methanol, ethanol, propan-2-ol, propan-1-ol, butan-1-ol, pentan-1-ol, hexadecan-1-ol, 2-phenyl ethanol, sec-phenyl ethanol, 3-phenyl-1-propanol, 1-phenyl-1-propanol, 2-phenyl-1-propanol, 2-phenyl-2-propanol, 1-phenyl-2-butanol, 2-phenyl-1-butanol, 3-phenyl-1-butanol, 4-phenyl-2-butanol, dl-1-phenyl-2-pentanol, 5-phenyl-1-pentanol, and 4-phenyl-1-butanol.~~

~~7. The method of claim 6, wherein the at least one alcohol comprises benzyl alcohol.~~

~~8. The method of claim 1, wherein the total sum concentration of the one or more alcohols in the liquid is about 0.01% v/v to about 10% v/v.~~

~~9. The method of claim 1, wherein the liquid further comprises at least one antioxidant agent and/or chelator.~~

~~10. The method of claim 9, wherein the liquid comprises at least one antioxidant agent and/or chelator in an amount sufficient to ameliorate the loss of binding capacity of the chromatography resin after exposure to the dose of gamma-irradiation.~~

~~11. The method of claim 10, wherein the liquid comprises at least one antioxidant agent~~two antioxidant agents are selected from the group consisting of: reduced glutathione, reduced thioredoxin, reduced cysteine, a carotenoid, melatonin, lycopene, tocopherol, reduced ubiquinone, ascorbate, bilirubin, uric acid, lipoic acid, a flavonoid, a phenolpropanoid acid, lidocaine, naringenin, fullerene, glucose, mannitol, 4-hydroxy-2,2,6,6-tetramethylpiperidin-1-oxyl, and dimethylmethoxy chromanol.

~~12~~7. The method of claim ~~11~~1, wherein the ~~liquid comprises~~ at least ~~one~~two antioxidant ~~agent~~agents are selected from the group consisting of: mannitol, sodium ascorbate, histidine, and methionine.

~~13~~8. The method of claim ~~12~~7, wherein the liquid comprises mannitol, sodium ascorbate, histidine, and methionine.

~~14~~9. The method of claim ~~11~~1, wherein the liquid comprises:

(i) between ~~75 mM and about 125 mM mannitol;~~

~~(ii) between 75 mM and about 125 mM methionine;~~

~~(iii) between 75 mM and about 125 mM sodium ascorbate;~~

~~(iv) between 75 mM and about 125 mM histidine;~~

~~(v) between~~ 30 mM and ~~about~~ 70 mM methionine and between ~~about~~ 30 mM and ~~about~~ 70 mM histidine; or

(~~v~~ii) between ~~about~~ 10 mM and ~~about~~ 50 mM methionine, between ~~about~~ 10 mM and ~~about~~ 50 mM histidine, and between ~~about~~ 10 mM and ~~about~~ 50 mM sodium ascorbate; or

(~~vi~~iii) between ~~about~~ 5 mM to ~~about~~ 45 mM sodium ascorbate, between ~~about~~ 5 mM and ~~about~~ 45 mM methionine, between ~~about~~ 5 mM and ~~about~~ 45 mM mannitol, and between ~~about~~ 5 mM to ~~about~~ 45 mM histidine.

~~15. The method of claim 11, wherein the liquid comprises at least one chelator selected from the group consisting of: ethylenediaminetetraacetic acid (EDTA), 2,3-dimercapto-1-propanesulfonic acid sodium (DMPS), dimercaptosuccinic acid (DMSA), metallothionin, and desferroxamine.~~

~~16~~10. The method of claim 1, wherein the chromatography resin is selected from the group consisting of: anionic exchange chromatography resin, cationic exchange chromatography resin, affinity chromatography resin, hydrophobic interaction chromatography resin, and size exclusion chromatography resin.

~~17~~11. The method of claim ~~16~~10, wherein the composition comprises affinity chromatography resin comprising a protein ligand.

~~18~~12. The method of claim ~~17~~11, wherein the protein ligand is protein A.

~~19~~13. The method of claim ~~16~~10, wherein the composition comprises an anionic exchange chromatography resin.

~~20~~14. The method of claim 13, wherein the anionic exchange chromatography resin comprises N-benzyl-N-methyl-ethanolamine groups.

15. The method of claim 1, wherein the dose of gamma-irradiation is between ~~about~~ 15 kGy ~~to about~~and 45 kGy.

~~21. A reduced bioburden chromatography resin produced by the~~16. The method of claim 1~~.~~

~~22. A method of making a reduced bioburden packed chromatography column~~, ~~further~~ comprising:

~~providing the reduced bioburden chromatography resin of claim 21; and~~

packing the chromatography resin into a reduced bioburden column in an aseptic environment.

~~23. A reduced bioburden packed chromatography column produced by the method of claim 22.~~

~~24. A reduced bioburden packed chromatography column produced by the method of claim 4.~~

~~25~~17. A composition comprising (i) a chromatography resin and (ii) a liquid comprising benzyl alcohol and at least ~~one alcohol~~two antioxidant agents, wherein the ~~at least one~~concentration of benzyl alcohol in the liquid is 0.01% v/v to 10% v/v, and wherein benzyl alcohol and the at least two antioxidant agents are present in ~~an amount~~amounts sufficient to ameliorate the loss of binding capacity of the chromatography resin upon treatment with a dose of gamma-irradiation sufficient to reduce bioburden of the composition.

~~26. A method of performing reduced bioburden column chromatography comprising:~~

~~(a) providing a reduced bioburden packed chromatography column of claim 23 or 24; and~~

~~(b) performing column chromatography using the reduced bioburden packed chromatography column and reduced bioburden buffer in a closed system.~~

~~27. An integrated, closed, and continuous process for reduced bioburden manufacturing of a purified recombinant protein comprising:~~

~~(a) providing a liquid culture medium comprising a recombinant protein that is substantially free of cells; and~~

~~(b) continuously feeding the liquid culture medium into a multi-column chromatography system (MCCS) comprising at least one reduced bioburden packed chromatography column of claim 23 or 24;~~

~~wherein the process utilizes reduced bioburden buffer, is integrated, and runs continuously from the liquid culture medium to an eluate from the MCCS that is the purified recombinant protein.~~

~~28. The process of claim 27, wherein the MCCS comprises at least two reduced bioburden packed chromatography columns.~~

~~29. The process of claim 27, wherein the MCCS is a periodic counter current chromatography system.~~

~~30. The process of claim 27, wherein the MCCS includes a plurality of columns for affinity or pseudo-affinity chromatography, cation exchange chromatography, anion exchange chromatography, or size exclusion chromatography, or any combination thereof.~~

~~31. An integrated, closed, and continuous process for reduced bioburden manufacturing of a purified recombinant protein comprising:~~

~~(a) providing a liquid culture medium comprising a recombinant protein that is substantially free of cells;~~

~~(b) continuously feeding the liquid culture medium into a first multi-column chromatography system (MCCS1);~~

~~(c) capturing the recombinant protein in the liquid culture medium using the MCCS1;~~

~~(d) producing an eluate from the MCCS1 that comprises the recombinant protein and continuously feeding the eluate into a second multi-column chromatography system (MCCS2);~~

~~(e) continuously feeding the recombinant protein from the eluate into the MCCS2 and subsequently eluting the recombinant protein to thereby produce the purified recombinant protein, wherein:~~

~~the process utilizes reduced bioburden buffer, is integrated, and runs continuously from the liquid culture medium to the purified recombinant protein, and~~

~~at least one column in the MCCS1 and/or MCCS2 contains a reduced bioburden packed chromatography column of claim 23 or 24.~~