What is claimed is:

1. A method for detecting anti-drug antibodies to a protein drug in a sample obtained from a subject that has been administered the protein drug, comprising:

incubating the sample under acidic conditions for a period of time to produce an acidified sample;

combining the acidified sample with a pH buffered solution comprising a target of the drug to produce target:drug complexes, wherein the target of the drug is labeled with a selectable label;

removing the target:drug complexes from the sample using the selectable label to produce a depleted sample;

incubating the depleted sample with an anti-target blocking reagent or an antigen binding fragment thereof and a biotinylated drug to produce an assay sample;

incubating the assay sample on an avidin-coated solid support;

washing the solid support after incubation with the assay sample to remove unbound anti-target blocking reagents;

adding the labeled target of the drug to the solid support;

washing the solid support to remove unbound labeled target; and

measuring a detectable signal from labeled target bound to the biotinylated drug bound to the solid support, wherein a decreased amount of signal from the solid support relative to a control sample indicates the presence of anti-drug antibodies in the sample.

2. The method of claim 1, wherein the anti-drug antibodies comprise neutralizing antibodies that specifically bind to the drug.

3. The method of claim 1 or 2, wherein the drug is an antibody or antigen binding fragment thereof or a fusion protein.

4. The method of claim 3, wherein the antibody is a monoclonal antibody, a bispecific antibody, an Fab fragment, an $F(ab')_2$ fragment, a monospecific $F(ab')_2$ fragment, a bispecific $F(ab')_2$, a trispecific $F(ab')_2$, a monovalent antibody, an scFv fragment, a diabody, a bispecific

diabody, a trispecific diabody, an scFv-Fc, a minibody, an IgNAR, a v-NAR, an hcIgG, or a vhH.

5. The method of claim 1, wherein the acidic conditions comprise a pH of 2.0 to about 4.0.

6. The method of claim 1, wherein the acidic conditions comprise a pH of 1 to 3.

7. The method of claim 1, wherein the selectable label comprises a magnetic label.

8. The method of claim 7, wherein the magnetic label is a paramagnetic label or a superparamagnetic label.

9. The method of claims 7 or 8, wherein the magnetic label is a metallic particle, metallic microparticle, metallic nanoparticle, metallic bead, magnetic polymer, uniform polystyrene spherical beads, or a superparamagnetic spherical polymer particle.

10. The method of claim 1, wherein the anti-target blocking reagent or the antigen binding fragment thereof specifically binds to the target of the protein drug.

11. The method of claim 1, wherein the drug tolerance of the method is at least 10 fold greater in the depleted sample compared to a non-depleted sample.

12. The method of claim 1, wherein the method positively identifies neutralizing antibodies (NAbs) in samples containing drug taken from the subject at least 29 days after administration of the protein drug.

13. The method of claim 1, wherein the sample is agitated during the incubation or washing steps.

14. The method of claim 1, wherein the labeled target is labeled with a fluorophore, a chemiluminescence probe, an electrochemiluminescence probe, a quantum dot, a rare earth transition metal, gold metal particles, silver metal particles, or a combination thereof.

15. The method of claim 14, wherein the label comprises ruthenium.

16. A method for identifying a lead protein drug comprising:

performing the method of claim 1 on a sample obtained from a subject to whom one or more protein drug candidates were administered; and

selecting, based on anti-drug antibodies (ADA) positivity and drug concentration respective to the detectable signal from the labeled target bound to the biotinylated drug bound to the solid support, the protein drug candidate that produces a higher proportion of the detectable signal from the solid support relative to a control sample, thereby being indicative of a lower presence of ADAs.