

Glossary

Aggregation the process in which misfolded proteins accumulate and clump together, reducing efficacy, and potentially increasing toxicity

Antisera human or animal sera containing antibodies against a specific antigen

Bioassay a laboratory procedure used to determine biological activity of a substance by comparing its effect on tissue or other living material with that of a standard preparation

Biobetters an improved version of an existing biologic, with a change in structure or formulation that leads to improved safety, efficacy and/or improved administration characteristics

Biopharming using genetically engineered crops or animals to produce proteins

Biosimilars officially approved versions of innovator biologic products that are highly similar to the innovator, with no clinically meaningful differences in safety and efficacy

Bovine derived from a cow or related animal

Chelating agent a compound that complexes metal ions

Chimeric antibody a recombinant antibody with reduced immunogenicity, containing domains from different species (most commonly mouse and human)

Denaturation the disruption of noncovalent bonds in a protein, resulting in the unfolding of the peptide chain, and a loss of some or all of the protein's specific characteristics

DNA ligase an enzyme that joins two separate DNA molecules together

DNA polymerase an enzyme that helps catalyze the polymerization of nucleotides into a DNA strand

Extrapolation regulatory principle that allows for the approval of a biosimilar for use in an indication held by the reference product but not directly studied in a comparative clinical trial with the biosimilar.

Follow-on biologics lower cost copies of innovator biologic products. May have been approved through FDA 505(b)(2) pathway, or as a biosimilar via the PHS 351(k) pathway.

- Fusion proteins** proteins created following the fusion of two or more genes that originally coded for separate proteins
- Glycosylation** the process of adding sugar units to proteins
- Human antibody** a recombinant antibody in which the mouse sequence has been completely removed and 100% human sequencing remains
- Human anti-mouse antibodies (HAMA)** antibodies that form a complex that is eliminated from the body, limiting the antibody from reaching its target receptor; an immune response, including fever, rash and potentially more serious side effects, typically accompanies HAMA
- Humanized antibody** a recombinant antibody, containing mostly human sequences with a small amount of mouse sequences; they have less affinity for the target than murine or chimeric antibodies but are less immunogenic
- Hybridoma** a hybrid cell used to produce monoclonal antibodies; formed by the fusion of a myeloma cell and an antibody-producing cell
- Immunogenicity** the ability of a substance to provoke an immune response
- Immunoglobulin** any of five classes of glycoprotein secreted by plasma cells that function as antibodies in the immune response
- Immunomodulator** a drug that affects the body's normal immune response in either a positive or negative fashion
- Immunosuppressant** a drug that lowers the body's normal immune response
- Intended copies** copies of innovator biologics that have not undergone comparative evaluations to the innovator, but which are being commercialized in some countries, and which may have clinically significant differences in formulation, dosages, efficacy or safety.
- Interchangeable biosimilar** a biosimilar deemed appropriate by a regulatory authority for substitution for the reference biologic under local laws and pharmacy practices
- Lyoprotectants** substances added to a formulation in order to protect the ingredients from the conditions involved in the freeze-drying process
- Myeloma** a tumor originating in the bone marrow; usually malignant
- Monoclonal antibody** one produced from a single cell line consisting of identical antibody molecules
- Murine antibody** an antibody derived from mouse proteins
- Neutralizing antibody** an antibody that reduces or abolishes the biological activity of an antigen, a microorganism, or a recombinant drug
- Neutropenia** abnormally low level of neutrophils, a particular type of white blood cell, in the blood
- PEGylation** the process of adding polyethylene glycol units to proteins or other macromolecules
- Peptide** moderately sized molecules consisting of up to 40 amino acid residues without higher order structure
- Pharmacogenomics** the study of how genetic variations affect response to drugs
- Plasmid** small, circular DNA molecules found inside bacterial cells
- Polyclonal antibodies** antibodies derived from different B-cell lines

Polymerase chain reaction (PCR) a technique used to quickly amplify DNA sequences *in vitro*

Porcine derived from a pig

Protein large molecules consisting of greater than amino acid 40 amino acid residues folded into secondary, tertiary or quaternary structures held together by peptide bonds

Quaternary structure protein structure characterized by the assembly of two or more monomeric macromolecules held together by noncovalent interactions

Recombinant DNA DNA genetically engineered to combine genetic material from two or more sources

Restriction endonuclease an enzyme that cuts DNA at a specific recognition sequence

Secondary structure protein structure characterized by the folding of a peptide chain into α helices, β sheets, or random coils

Serum therapy administration of serum obtained from an immunized animal in order to treat disease

Site-directed mutagenesis a genetic engineering technique that creates a mutation at a defined site in a DNA molecule in order to change the properties of the resultant proteins

Tertiary structure protein structure characterized by the folding of α helices and β sheets into a three-dimensional structure held in place by hydrophobic and hydrophilic interactions

Thrombocytopenia a deficiency of platelets in the blood

Transgenic containing genetic material from another species

Totality of evidence the approach used to demonstrate similarity between biosimilar and innovator biologic, which relies most heavily on analytical studies. No one study is pivotal, and an orthogonal approach is needed, whereby each quality attribute is measured by multiple analytical methods.

Index

A

Abatacept, 79
Abciximab, 82
Absorption
 intramuscular, 67
 intravenous, 67
 intravitreal, 67
 subcutaneous, 67
Actemra, 80
Adalimumab, 79
Adalimumab-adbm, 90
Adalimumab-atta, 90
Adcetris, 76
Ado-trastuzumab emtansine, 70, 76
Adsorption of proteins, 46
Affordable Care Act, 89
Aflibercept, 76, 82
Afrezza[®], 48
Aggregation, 32
Aimovig, 82
Alefacept, 83
Alemtuzumab, 76, 80
Alirocumab, 70, 82
Alternative protein scaffolds, 66
Alzheimer's disease (AD), 49
Amevive, 83
Amjevita, 90
Anthem, 82
Antibody drug conjugates (ADC), 64–65
Antibody engineering
 ADC, 64–65
 alternative protein scaffolds, 66
 biospecific antibodies, 65, 66
 Fc region, 63
 fusion proteins and antibody fragments, 64

Antibody fragments, 64
Antibody structure
 Fab, 57
 Fc region, 57
 Fv, 57
 heavy chains, 57
 light chains, 57
Antibody-dependent cellular cytotoxicity (ADCC), 63
Antidrug antibodies (ADAs), 39
Antigen-binding fragment antivenoms (FabAV), 56
Antithrombin III, 7
Arcalyst, 80
Arzerra, 70, 76
Atezolizumab, 77
Autoimmune disorders, 77–78
Avastin, 70, 76
Avelumab, 77

B

Basaglar[™], 89
Basiliximab, 75
Bavencio, 77
Becaplermin, 51
Belatacept, 75
Belimumab, 80
Benlysta, 80
Benralizumab, 82
Berinert[®], 10
Bevacizumab, 70, 76
Bevacizumab-awwb, 90
Bexxar[®], 62, 76, 83
Bezlotoxumab, 82

Bioassays, 19
 Bioavailability, 40
 Biologics, analysis and regulation, 87, 91
 biosimilar, 87, 90, 91, 93
 FD&C Section 505(b)(2) (*see* FD&C Section 505(b)(2))
 innovator biologics, 89
 interchangeability, 93, 94
 marketplace uptake, 95
 PHS Act/BCPI Act, 89
 product naming, 94
 product switching, 94
 totality of the evidence (*see* Totality of the evidence)
 Biologics License Application (BLA), 89
 Biologics Price Competition and Innovation (BCPI) Act, 89
 Biopharming, 5
 Biosimilar, 1, 87
 Biosimilar product naming, 94
 Biosimilar product switching, 94
 Biosimilarity
 definition, 93
 demonstration, 92
 FDA, 90, 91
 marketplace uptake, 95
 totality, evidence, 89
 Bispecific antibodies, 65
 Blinatumomab, 77
 Blincyto, 77
 Brentuximab vedotin, 76
 Brodalumab, 80
 Buccal, 50
 Burosumab-twza, 82

C

C1 esterase inhibitor (C1INH), 7, 10
 Calcitonin, 49
 Campath-1H, 76
 Canakinumab, 80
 Cancer
 chemotherapy, 74
 lymphoma cells, 75
 thyroid protective premedication, 75
 yttrium-90 component, 75
 Cardiotoxicity, 74
 Cell culture, 5
 Cell lysis, 63
 Center for Biologics Evaluation and Research (CBER), 56
 Cerezyme[®], 10
 Certolizumab Pegol, 79
 Cetuximab, 70, 76

Chemical instabilities of proteins, 37
 Chemical modification
 EPO, 16
 fusion proteins, 14
 glycosylation, 14
 immunoglobulin, 14
 PEG, 16
 PEGylation, 14
 site-directed mutagenesis, 14
 tenecteplase, 14
 therapeutic proteins, 15
 TNF receptor, 14
 Chimeric antibodies, 60
 Cimzia, 79
 Cinqair, 82
 Circular dichroism (CD), 21
 Cloning
 daughter cells, 2
 DNA ligase, 4
 frog DNA, 2
 molecular cloning, 4
 rDNA molecule, 3
 restriction endonucleases, 3
 Cohen-Boyer method, 4
 Complementarity-determining region (CDR), 57
 Complement-determined cytotoxicity (CDC), 63
 Conestat alfa, 10
 Cosentyx, 80
 Crysvida, 82
 Cyltezo, 90
 Cynryze[®], 10
 Cyramza, 77
 Cystic fibrosis (CF), 45
 Cytokine release syndrome (CRS), 70, 71

D

Daclizumab, 75, 81, 83
 Daratumumab, 77
 Darbapoetin, 16
 Darzalex, 77
 Deamidation, 38
 Defense Advanced Research Projects Agency (DARPA), 9
 Denaturation, 33
 Denileukin diftitox, 14
 Denosumab, 70, 76, 82
 Differential scanning calorimetry, 23
 Dinutuximab, 77
 Distribution, 67
 DNA ligase, 4
 DNA polymerase, 12
 Dornase alpha, 45
 Drug development, *see* Antibody engineering

Dupilumab, 80
Dupixent, 80
Dynamic light scattering (DLS), 23

E

Eculizumab, 82
Efalizumab, 81, 83
Electrospray ionization (EI), 22
Elelyso[®], 10
Elimination, 68
Elotuzumab, 77
Emicizumab-kxwh, 82
Empliciti, 77
Enbrel[®], 14, 79
Endocytosis, 39
Entyvio, 80
Enzyme-linked immunosorbent assay (ELISA), 19
Epoetin alfa-epbx, 90
Erbitux, 70, 76
Erelzi, 90
Erenumab-aooe, 82
Erythropoietin (EPO), 16, 40
Etanercept, 14, 79
Etanercept-szszs, 90
European Union (EU), 95
Evolocumab, 70, 82
Excipients, 46–47
Exclusivity period, 90
External pump systems, 43
Extrapolation of data, 91, 93
Exuber[®], 48
Eylea, 82

F

Fab region, 57
Fazenra, 82
FD&C Section 505(b)(2)
 biotechnology-derived drug, 88
 FDA, 88
 FOB, 88
 generic biologic, 88
 Genotropin[®], 89
 insulin glargine, 89
 Lantus[™], 89
 Lusduna[™], 89
 Omnitrope[®], 89
 Public Health Service Act, 87
 recombinant protein, 88
 Somatotropin, 89
Filgrastim-sndz, 90
Fluorescence, 20

Follow-on biologic (FOB), 88
Fortical[®], 49
Fourier transform infrared (FTIR), 21
Fragment, antigen binding (Fab), 57
Fragment, crystallizable (Fc), 57
Fragment, variable (Fv), 57
Freeze-drying, 43
Fulphila, 90
Fumaryl diketopiperazine (FDKP), 48
Fusion proteins, 14

G

Gazyva, 70, 77
Gel electrophoresis, 20
Gemtuzumab ozogamicin, 62, 76, 83
Genotropin[®], 89
Glomerulonephritis, 55
Glycosylation, 41, 42
 chemical modification, 14
 molecular cloning, 4
 therapeutic proteins, 15
Golimumab, 79
Granix[™], 90
Guselkumab, 80

H

Haegarda[®], 10
Harvard mouse, 6
Heavy chain, 57
Heavy metals, 38
Hemlibra, 82
Herceptin, 70, 76
High performance liquid chromatography (HPLC), 23
Human antibody, 61
Human anti-chimeric antibodies (HACA), 61
Human anti-human antibodies (HAHA), 61
Human anti-mouse antibodies (HAMA), 60
Human serum albumin (HSA), 64
Humanized antibodies, 61
Humira, 79
Hybridoma, 56
Hydrolysis, 37

I

Ibrutumomab tiuxetin, 62, 70, 76
Idarucizumab, 82
Ilaris, 80
Imiglucerase, 10
Immunoassays, 19

- Immunogenicity of proteins and peptides, 39–40
 Immunoglobulin, 14, 56
 Inflectra, 90
 Infliximab, 79
 Infliximab-abda, 90
 Infliximab-dyyb, 90
 Infliximab-qbtx, 90
 Injectable delivery
 chemical modification, 42
 external pump systems, 43
 freeze-drying, 43
 glycosylation, 42
 intravenous injection, 42
 liquid formulations, 44
 lyophilization, 43, 44
 lyoprotectants, 44
 non-injectable protein formulations, 45
 patch-pump, 43
 PEGylation, 42
 pen injectors, 43
 primary drying, 44
 protein and peptide drugs, 42
 protein formulations, 45
 recombinant antihemophilic factors, 42
 secondary drying, 44
 spray drying, 43
 tissue plasminogen activators, 43
 Instability, 32
 Insulin, 49
 Insulin glargine, 89
 Interchangeability, 93
 Interchangeable biosimilar, 94
 Interferon, 16
 Ipilimumab, 70, 76
 Isothermal titration calorimetry (ISC), 23
¹³¹I-tositumomab, 62, 76, 83
 Ixekizumab, 80
 Ixifi, 90
- J**
 John Cunningham virus (JCV), 72
- K**
 Kadcyla, 70, 76
 Kanuma™, 11
 Kevzara, 80
 Keytruda, 70, 77
- L**
 Lactoferrin, 7
 Lantus™, 89
 Lartruvo, 77
 Lemtrada, 80
 Light chains, 57
 Light scattering, 22
 Lucentis, 70, 82
 Lusduna™, 89
 Lyophilization, 43
 Lyoprotectants, 44
 Lysosomal acid lipase (LAL), 11
- M**
 Malignancies, 73
 Mass spectrometry, 22
 Matrix-assisted laser desorption ionization (MALDI), 22
 Mechanical denaturation of proteins, 35
 Mepolizumab, 82
 Metabolism, 68
 Miacalcin®, 49
 Molecular cloning, 4, 10
 biopharming, 5, 6, 8
 Elelyso®, 10
 Ruconest®, 10
 C11NH, 10, 11
 cell culture, 5, 8
 Cohen-Boyer method, 4
 DARPA, 9
 daughter cell, 4
E. coli, 5
 FDA, 6, 7
 fermentation tank, 5
 glucose-based treatment, 9
 glycosylation, 4
 Harvard mouse, 6
 LAL, 11
 milk yield, 7
Nicotinia benthamiana, 9
 post-translational modifications, 4
 Ruconest®, 11
 transgenic animals, 5
 transgenic plants, 5–7
 transgenic rice, 8
 ZMapp, 9
 Molecular target, 32
 Monoclonal antibodies, 55
 Monoclonal antibody nomenclature
 components, 57
 ¹³¹I-tositumomab, 59
 substem A, 59
 substem B, 59, 60
 Monoclonal antibody types
 chimeric, 60, 61
 human, 61

humanized, 61
murine, 60
Monomethyl auristatin E (MMAE), 65
Mucocutaneous reactions, 73
Murine antibodies, 60
Muromonab-CD3, 75, 83
Mvasi, 90
Mylotarg[®], 62, 76, 83

N

Nasal delivery, 49
Natalizumab, 79
Necitumumab, 70, 77
Neutralizing antibodies (NABs), 39
New Animal Drugs, 7
Nicotinia benthamiana, 8
Nivolumab, 70, 77
N-linked oligosaccharides, 63
Nucala, 82
Nulojix, 75

O

Obiltoximab, 82
Obinutuzumab, 70, 77
Ocrelizumab, 80
Ocrevus, 80
Ofatumumab, 63, 70, 76
Ogivri, 90
Olaratumab, 77
Omalizumab, 82
Omnitrope[®], 89
Ontak[®], 14
Opdivo, 70, 77
Opportunistic infections, 72
Oral delivery, 41
Oral-Lyn[®], 50
Orencia, 79
Organ transplant prophylaxis, 74
Oromucosal delivery, 50
Orthogonality, 91
Orthoclone OKT3, 75, 83
Oxidation, 38

P

Palivizumab, 70, 81, 82
Panitumomab, 70, 76
Patch-pump, 43
Pegasys[®], 42
Pegfilgrastim-jmdb, 90
PEG-Intron[®], 42
PEGylation, 14, 42
Pembrolizumab, 70, 77

Pen injectors, 43
Peptides, 31
Perjeta, 70, 76
Permeability
ADAs, 39
endocytosis, 39
immunogenicity, 39–40
immunologic response, 40
NABs, 39, 40
protein and peptide, 39
Pertuzumab, 70, 76
PHS Act 351(k), 89
Physical instabilities, 32, 39
Polyethylene glycol (PEG), 16
Polymerase chain reaction (PCR), 4
DNA polymerase, 12
DNA sequence, 12, 13
forensic science, 13
human genes, 12
Thermus aquaticus, 12
Portraza, 70, 77
Post-translational modifications, 4
Praluent, 70, 82
Praxbind, 82
Precipitation, 32
Product switching, 94
Progressive multifocal leukoencephalopathy (PML), 72, 73, 81
Prolia, 70, 82
Protein characterization, 19, 20, 22–24
Protein drug deliver, 49
Protein stability, 38
Proteins, 31
Public Health Service (PHS) Act, 89
Pulmonary delivery
Afrezza[®], 48
bioavailability, 45
CF, 45
dornase alpha, 45
Exubera[®], 48
FDKP, 48
Pulmozyme[®], 45
spray-drying process, 48
Pulmozyme[®], 45
Purple Book, 90

R

Radioconjugates, 65
Raman spectroscopy, 22
Ramucirumab, 77
Ranibizumab, 70, 82
Raptiva, 83
Raxibacumab, 82
rDNA molecule, 3

- Reactivation of tuberculosis, 72
 Recombinant antihemophilic factors, 42
 Recombinant DNA (rDNA), 2
 Recombinant DNA technology, 1, 2, 4, 12, 14
 analysis and regulation, 24
 bioassays, 19
 calorimetry, 23
 CD, 21
 cell disruption methods, 17
 chemical modification (*see* Chemical modification)
 chromatography methods, 18
 cloning (*see* Cloning)
 DLS, 23
 electrophoresis, 20
 fluorescence, 20, 21
 formation, 3
 FTIR, 21
 glycosylation, 15
 HPLC, 23, 24
 immunoassays, 19
 light scattering, 22
 mass spectrometry, 22
 molecular cloning (*see* Molecular cloning)
 PCR (*see* Polymerase chain reaction (PCR))
 PEGylation, 17
 purification, 16, 17
 Raman spectroscopy, 22
 ultraviolet/visible spectroscopy, 20
 Regranex[®], 51
 Remicade, 79
 Renflexis, 90
 ReoPro, 82
 Repatha, 70, 82
 Reslizumab, 82
 Restriction endonucleases, 3
 Retacrit, 90
 Reversed-phase HPLC (RP-HPLC), 24
 Riloncept, 80
 Rituxan, 70, 76, 79
 Rituximab, 59, 70, 76, 79
 Ruconest[®], 10
- S**
- Sarilumab, 80
 Sebelipase alfa, 7
 Secukinumab, 80
 Serum sickness, 55
 Serum therapy, 55
 Siliq, 80
 Siltuximab, 82
 Simponi, 79
 Simulect, 75
 Site-directed mutagenesis, 14
- Size exclusion chromatography (SEC), 24
 Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), 20
 Soliris, 82
 Somatotropin, 89
 Spray drying, 43
 Stelara, 80
 Stevens-Johnson syndrome (SJS), 73
 Sublingual, 50
 Substem A, 59
 Substem B, 59
 Surfactants, 36
 Sylvant, 82
 Synagis, 70, 82
- T**
- Taliglucerase, 7
 Taltz, 80
 Tbo-filgrastim, 90
 Tecentriq, 77
 Technosphere[™], 48
 Tenecteplase, 14
 Therapeutic proteins, 3, 34, 39, 42, 45
 adsorption, 36, 37
 antibody formation, 41
 bioavailability, 40
 chemical instabilities, 37
 deamidation, 38
 excipients, 46–47
 hydrolysis, 37
 injectable delivery (*see* Injectable delivery)
 instability, 32
 mechanical denaturation, 35
 nasal delivery, 49
 nebulizer/compressor systems, 48
 oral delivery, 41
 oromucosal delivery, 50
 oxidation, 38
 permeability (*see* Permeability)
 physical instabilities, 32, 33
 protein aggregation, 36
 protein/peptide, 31–33
 pulmonary delivery (*see* Pulmonary delivery)
 recombinant technology, 31
 thermal denaturation
 crystallization, 34
 temperatures, 34
 topical delivery, 51
 transdermal delivery, 50
 Thermal denaturation of proteins, 34
Thermus aquaticus, 12
 Tissue plasminogen activators, 43
 TNF receptor, 14
 Tocilizumab, 80

Topical delivery, 51
Totality of the evidence, 89, 90
 analytical test, 91
 biosimilar, 92, 93
 extrapolation of data, 93
 FDA, 92
 innovator products, 91
 orthogonality, 91
 PHS Act 351(k), 91
Toxic epidermal necrolysis (TEN), 73
Transdermal delivery, 50
Transgenic animals, 5
Transgenic plants, 5
Transgenic rice, 8
Trastuzumab, 70, 76
Trastuzumab-dkst, 90
Tremfya, 80
Tumor lysis syndrome (TLS), 72
Tumor necrosis factor (TNF), 14
Type I hypersensitivity, 71
Tysabri, 79

U

Ultraviolet/Visible Spectroscopy, 20
Unituxin, 77
Ustekinumab, 80

V

Vectibix, 70, 76
Vedolizumab, 80
Vibrational spectroscopy, 21

W

Western blotting, 20

X

Xgeva, 70, 76, 82
Xolair, 82

Y

Yervoy, 70, 76

Z

Zaltrap, 76
Zarxio, 90
Zenapax, 75, 83
Zevalin[®], 62, 70, 76
Zinbryta, 83
Zinplava, 82
ZMapp, 9