



A Glossary of Terms Used in the Biotherapeutic Industry

Technical Overview

A

adaptive immune response

The response of antigen-specific lymphocytes to antigen.

ADC

Antibody-drug conjugates are complex molecules composed of an antibody linked to a biological active anticancer drug.

ADME

Absorption, distribution, metabolism, and excretion (ADME) describes the processes that affect a pharmaceutical compound as it passes through an organism.

affinity

Attraction between particles or substances; relatively speaking, a measure of the attraction of one molecule toward another.

aggregate

A clustered mass, as of protein molecules; or to cluster together in such a way.

albumins

Protein constituents of blood plasma and serum also found in muscle, egg white, and milk.

alkylation

The introduction by substitution or addition, of an alkyl group into an organic compound; alkylating agents are various substances that contain an alkyl radical and that can, therefore, replace a hydrogen atom in an organic compound; alkylation is used to prevent refolding of already reduced proteins during peptide mapping.



***alpha* helix (α -helix)**

A coil or spiral element of a protein's secondary structure.

amino acids

A class of 20 naturally occurring hydrocarbon molecules that combine to form proteins in living things. They include alanine (A), aspartic acid or asparagine (B), cysteine (C), glutamic acid (Z) or glutamine (Q), phenylalanine (P), glycine (G), histidine (H), isoleucine (I), lysine (K), leucine (L), methionine (M), proline (P), arginine (R), serine (S), threonine (T), valine (V), tryptophan (W), and tyrosine (Y). (Those are the so-called normal amino acids; others have been synthesized and are used in medicinal chemistry). They are incorporated into proteins by transfer RNA according to the genetic code.

amphoteric

A substance that has both acid and base properties. Amphoteric molecules can accept or donate protons to act as an acid or a base.

antibody

Protein molecules produced by the immune system. Antibodies recognize foreign molecules or structures such as bacteria, viruses, and various antigens to which the body has been exposed.

antigen

Any agent that reacts specifically with an antibody. Antigens can contain more than one site capable of binding to a particular antibody. See immunogen.

antigenicity

The capacity of a substance to induce the formation of antibodies or to elicit an immune response when injected into an animal.

antiserum

The fluid component of clotted blood from an immune individual that contains antibodies against the molecule used for immunization.

API

Active pharmaceutical ingredient (API). See drug substance.

B

base

One of the molecules - adenine (A), guanine (G), cytosine (C), thymine (T), or uracil (U) - which form part of the structure of DNA and RNA molecules. The order of bases in a DNA molecule determines the structure of proteins encoded by that DNA. See nucleotide.

base pair

Two bases on different strands of nucleic acid that join. In DNA, cytosine always pairs with guanine, and adenine always links to thymine. In RNA molecules, adenine joins to uracil.

***beta* sheet (β -sheet)**

A structure resulting from the regular, accordion-like folding of polypeptide chains; the chief alternative to the *alpha* helix.

bioactivity

A protein's ability to function correctly after it has been delivered to the active site of the body (*in vivo*).

bioavailability

A measure of the rate and the total amount of drug that reaches the target tissue after administration.

Biobetter

A biopharmaceutical that is significantly different in structure, form, and function from the innovator product.

biogeneric

A biopharmaceutical that is produced and licensed by a different company than the one that originally licensed it. A biogeneric is used for the same indications, and may be produced by a substantially similar process, or one that is different, but results in comparable product. See also biosimilar.

biologics

Products of living organisms used in the prevention or treatment of disease.

biomarker

A physiological event or molecule that can be measured. Examples include the presence or absence of a protein or a mutated gene. Biomarkers are often used to indicate the presence or progression of a disease.

biosciences

A term that encompasses both biotech and pharmaceutical companies.

biosimilar

A biopharmaceutical that is produced using a different cell line or master cell bank or different process, yet meets criteria for comparability in clinical activity. A biosimilar may differ in its purity/impurity profile, and its potency may differ in a definable way. See also biogeneric and follow-on biologic.

BLA

Biologics license application; the required application for marketing a biologic product in the United States. Most biotechnology-derived drugs are approved through a BLA, rather than an NDA, although some biologics, such as recombinant insulin and human growth hormone, considered to be simpler in structure and well-characterized, have been approved under NDAs.

bulk active ingredient

Also bulk drug substance, the active ingredient that is formulated with excipients to produce the drug product formulation. Biopharmaceuticals are produced "in bulk" through bioprocessing.

C

CBER

Center for Biologics Evaluation and Research at the US FDA. CBER regulates vaccines, gene therapy, cellular products, allergenic extracts, antitoxins, antivenoms, venoms, blood, and blood products (clotting factors and plasma-derived products).

CDER

Center for Drug Evaluation and Research. The largest of FDA's six centers, CDER regulates prescription and over-the-counter drugs, and therapeutic proteins and monoclonal antibodies for use *in vivo*.

cGMP

Current good manufacturing practice, see GMP.

change control

A system by which changes to facilities, equipment, and processes are documented and approved. The change control system ensures that changes are evaluated and approved prior to implementation to maintain the facilities, equipment, and processes in a validated state.

chaotropic

Disrupting the structure of water, macromolecules, or living systems to promote activities that would have been inhibited by these factors. Urea and guanidine hydrochloride are common chaotropic agents used with proteins.

characterization

Precisely deciphering and describing an entity's properties (physical and chemical properties for a molecular entity; genetic and stability properties for a cell line).

chemokine

Signaling molecules that are involved in the activation and migration of immune system cells. Chemokine signaling plays a key role in the inflammatory response.

chimeric antibody

Antibodies whose gene sequence consists of DNA from two different species. Typically, the term refers to antibodies whose DNA is between 10% and 25% mouse origin, with the remaining sequence being human origin.

C-terminal

Carboxyl-terminal; the carboxyl terminus of a protein chain, with a free carboxyl group.

clinical trial

The process of bringing a drug to market. Phase I trials are initial studies to determine the metabolism and pharmacologic actions of drugs in humans, side effects associated with increasing doses, and to gain early evidence of effectiveness. In Phase II, controlled clinical studies evaluate drug effectiveness for patients with the disease and determine the common short-term side effects and risks. Phase III trials are expanded investigations to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide an adequate basis for physician labeling.

codon

A set of three nucleotide bases in a DNA or RNA sequence, which together code for a unique amino acid. For example, AUG (adenine, uracil, and guanine) codes for the amino acid methionine.

D

deamidation

Removal of one or more amide groups from the Gln or Asn residue in a protein, converting the residues to Glu, Asp, or isoAsp. Depending on the protein, this may have no effect, or major effects, on potency, stability, or solubility.

denaturation

A condition in which a protein unfolds or its polypeptide chains are disordered, rendering the molecules less soluble and usually nonfunctional.

denature

To unfold a protein or break it up, changing its usual three-dimensional structure. Proteins can be denatured by chemical action, heat, or even agitation of a protein solution.

denatured protein

A protein having unfolded or disordered polypeptide chains, which render the molecule less soluble and usually nonfunctional. Sometimes a denatured protein can be refolded (renatured).

dimer

A polymer made up of two identical molecules. When three molecules link up, the resultant polymer is called a trimer. Larger polymers are usually referred to by placing a number before the "-mer" suffix: 4-mer, 5-mer, 6-mer, and so on.

disulfide bond

A covalent bond formed between sulfur atoms of different cysteines in a protein; such bonds (links, bridges) help hold proteins together.

DNA

Deoxyribonucleic acid, the nucleic acid based on deoxyribose (a sugar) and the nucleotides G, A, T, and C. Double-stranded DNA has a corkscrew-ladder shape (the double helix) and is the primary component of chromosomes, which thus carry inheritable characteristics of life. See nucleotides and nucleic acids.

downstream processing

The phase of a biomanufacturing campaign that consists of harvesting, purifying, and formulating the product.

drug candidate

A small molecule or biologic that is being tested for its therapeutic potential.

drug development

The process of testing therapeutic molecules for safety and efficacy in animals and humans, and developing appropriate formulation, delivery, and manufacturing methods.

drug discovery

The process of identifying molecules with a therapeutic effect against a target disease.

drug substance

Also known as active pharmaceutical ingredient (API); the active drug chemical or biological substance in purified bulk form. The drug substance is further processed to derive a drug product.

E

E. coli

Escherichia coli is a common gut bacterium that has been studied intensively by geneticists because of its small genome size, normal lack of pathogenicity, and ease of growth in the laboratory.

efficacy

The ability of a substance (such as a protein therapeutic) to produce a desired clinical effect; its strength and effectiveness; usefulness; the power to produce an effect.

enzymes

Proteins that catalyze biochemical reactions by causing or speeding up reactions without being changed in the process themselves.

epitope

A molecular region on the surface of an antigen that elicits an immune response and can combine with the specific antibody produced by such a response; also called a determinant or an antigenic determinant.

excipient

A type of raw material that is present in the drug product and, thus, has direct patient contact; includes inert materials such as bulking agents, stabilizing agents, preservatives, salts, solvents, or water. An excipient must be evaluated for safety in animals, unless it has been approved as GRAS, or is on a list of approved excipients.

express

To translate a cell's genetic information, stored in its DNA (gene), into a specific protein.

expression system

A host organism combined with a genetic vector (such as a virus or circular DNA molecule called a plasmid) that is loaded with a gene of interest. The expression system provides the genetic context in which a gene will function in the cell, that is, the gene will be expressed as a protein.

expression vector

A virus, plasmid, cosmid, or artificial chromosome that delivers foreign genes to a host, creating a recombinant organism that will express the desired protein.

F**Fab**

Antigen-binding fragment of an immunoglobulin. An IgG Fab is prepared by enzymatic cleavage of the intact tetrameric IgG, and reduction of the interchain disulfide links, and binds one mole of antigen per mole. See F(ab)'₂.

F(ab)'₂

Dimeric antigen-binding fragment of an immunoglobulin. An IgG F(ab)'₂ is prepared by enzymatic digestion of an intact IgG, which removes the Fc portion of the molecule. F(ab)'₂ binds two moles of antigen per mole. See Fab.

FAb

Fragment antigen binding site. Antibodies are Y-shaped molecules. The arms of each Y are the FAb regions that bind to antigens; the stem of the Y is the Fc region, which attracts microbe-engulfing cells to destroy what has been bound. If the active part of an antibody can be identified, sometimes only that part of it may be needed as a therapeutic molecule (facilitating production and processing by reducing the size and lessening the chances of an immune response in patients who receive the drug). This fragment may be conjugated to another molecule (such as PEG) for stability or other reasons.

Fc

Portion of an immunoglobulin molecule that carries various effector functions, such as the ability to bind complement. Important in immunological activities, and separable from the antigen-binding portion by enzymatic or chemical cleavage. See Fab.

FDA

US Food and Drug Administration.

folding

A process in which a protein spontaneously forms into its correct, knotted tertiary structure that is held in place by chemical bonds and by attractive forces between atoms.

follow-on biologic

Another term for biosimilar or biogenetic.

formulation

The process by which different chemical substances, including the active drug, are combined to produce a final medicinal product.

G**gene**

The unit of inheritance consisting of a sequence of DNA occupying a specific position within the genome. Three types of genes have been identified: structural genes encoding particular proteins; regulatory genes controlling the expression of the other genes; and genes for transfer RNA or ribosomal RNA instead of proteins.

gene therapy

Treats, cures, or prevents disease by changing the expression of a person's genes or inserting genes into the genome. Current gene therapy is primarily experimental, with most human clinical trials only in the research stages. Gene therapy can target somatic (body) or germ (egg and sperm) cells. In somatic gene therapy, the recipient's genome is changed, but the change is not passed along to the next generation. In germ-like gene therapy, the parent's egg and sperm cells are changed with the goal of passing on the changes to their offspring.

genetic engineering

Altering the genetic material of cells or organisms to make them capable of producing new substances or performing new functions.

genome

All of the genetic material in the chromosomes of a particular organism.

genomics

The application of recombinant DNA, DNA sequencing methods, and bioinformatics to sequence, assemble, and analyze the function and structure of the genome.

GLP

Good laboratory practice. According to 21 CFR Part 58, regulations to ensure quality of nonclinical laboratory studies related to safety. All activity is recorded, trained staff use only established procedures, and records and samples are maintained.

glycoproteins

Proteins that contain carbohydrate, sugar, side chains added as a post-translational process; presence of sugar side chains often affects activity and *in vivo* stability.

glycosylation

Adding one or more carbohydrate molecules onto a protein (a glycoprotein) after it has been built by the ribosome; a post-translational modification.

GMO

A genetically modified organism (GMO) is one in which the DNA has been altered using genetic engineering techniques.

GMP

Good manufacturing practice. According to 21 CFR Parts 210, 211, 600, 610, and (for devices) 820, current good manufacturing practices (cGMPs) influence the manner in which biopharmaceuticals and other drugs and medical devices are produced. Standard operating procedures must be followed, processes must be validated, equipment must be qualified, and properly trained staff must maintain a clean/sterile environment.

Golgi body

A cell organelle consisting of stacked membranes where post-translational modifications of proteins are performed; also called Golgi apparatus.

GRAS

Generally recognized as safe is a US FDA designation that a chemical or substance added to food is considered safe by experts, and so is exempt from the usual Federal Food, Drug, and Cosmetic Act (FFDCA) food additive tolerance requirements.

H

high throughput screening

HTS is an automated trial-and-error testing, typically using robotics, of very large sets of chemicals or materials.

hybridization

The process of joining complementary strands of DNA to make an RNA-DNA hybrid. The partial pairing of DNA single strands from genetically different sources.

hydrophilic

Having an affinity for water; attracting, dissolving in, or absorbing water; readily absorbing moisture; having strongly polar molecular groups that readily interact with water.

hydrophobic

Insoluble in water; the extent of insolubility; not readily absorbing water; resisting or repelling water, wetting, or hydration; or being adversely affected by water.

I-J

immunogen

A substance that provokes an immune response, that is, the body recognizes it as a foreign agent that must be expelled or destroyed.

in vitro

Performed using laboratory apparatus rather than a living animal.

in vivo

Involving living animals or humans as test subjects.

intermediates

Substances formed in the middle stages of a series of processing steps; stepping stones between a parent substance and a final product.

investigational new drug

INDs are drugs that have gained FDA approval to be shipped across state lines, typically for clinical trials, but has not yet gained approval for marketing.

K-L

large molecule drug

Another name for protein therapeutics. Large molecule drugs are too large to enter cells.

ligase

An enzyme that causes molecular fragments (such as DNA, RNA, or peptides) to link together; DNA ligase is used with restriction enzymes to create recombinant DNA.

light-scattering analysis

Analytical method that gives information about the size and shape of molecules based on how they disperse ultraviolet and visible light.

M

MAB

Monoclonal antibody; a highly specific, purified antibody that recognizes only a single epitope.

metabolome

This is the full complement of small-molecule metabolites (such as metabolic intermediates, hormones and other signaling molecules, and secondary metabolites) that are found within a biological sample or organism.

metabolomics

The study of the metabolome.

microheterogeneity

In biopharma, usually small differences in the amino acid sequence or structure of a polypeptide chain. For example, to produce a recombinant protein in *E. coli*, a methionine (Met) must be added to one end of the protein sequence to act as a signal that initiates protein synthesis. In most cases, Met is removed once the protein is made. Sometimes the Met is removed for only some of the molecules. The purified product is then a mixture of a protein with the native sequence and a protein with the native sequence plus the extra amino acid.

mRNA

Messenger RNA; which serves as a template for protein synthesis. It is made as a complement to a DNA sequence and then transported from the cell nucleus to the ribosomes.

multimer

Any small polymer; in biopharma, usually a protein made up of more than one polypeptide chain.

N

native

The natural nondenatured state exhibiting biological activity; in biopharma, it usually refers to a molecule's normal three-dimensional structure under optimal conditions.

NBE

New biological entities are proteins, peptides, antibodies, viruses, and vaccines that prevent or treat disease. NBEs are significant because they can be active against all extracellular targets.

NDA

New drug application; CDER's equivalent of the BLA. It is used for small-molecules and some biopharmaceuticals (such as hormones and small peptides), which are regulated by CDER rather than CBER.

N-terminal

Amino-terminal or amine terminus; the amine terminus of a protein chain (with a free α -amino group).

nucleic acids

DNA or RNA: chainlike molecules composed of nucleotides.

nucleotides

Molecules composed of a nitrogen-rich base, phosphoric acid, and a sugar. The bases can be adenine (A), cytosine (C), guanine (G), thymine (T), or uracil (U).

O

oxidation

Chemical reaction in which a compound or atom loses valence electrons, due to reaction with an oxidizing agent (for example oxygen, peroxides, metal ions, or others). Many proteins are prone to oxidation on exposure to air (such as oxidation of the methionine (Met) amino acid into methionine sulfide or sulfone). See also redox.

P

PAT

Process analytical technology; an FDA initiative that seeks to encourage industry to develop and use new analytical technology and multivariate analyses as part of risk management during process development, manufacturing, and quality control testing. PAT includes on-line, real-time analyses, process control tools, continuous improvement and knowledge management tools, and statistical tools.

PEGylation

Covalent attachment of polyethylene glycol molecule(s) to a protein molecule through selected amino acid side groups, for example free amino or sulfhydryl groups. May be done to decrease toxicity or improve its solubility and circulating half-life in the body.

peptide bond

The carbon-nitrogen covalent bond (link) between an amino group of one amino acid and a carboxyl group of another, formed by removing water and resulting in the group RCO-NH. This linkage does not allow free rotation, and it is the important bond that connects amino acid monomers to form the polymer known as a polypeptide.

peptide mapping

Bioanalytical method in which proteins are selectively cleaved by enzymes to create a characteristic pattern of peptides that is elucidated through chromatographic separations and spectroscopic or spectrometric detection.

peptides

Proteins consisting of fewer than 40 amino acids.

pharmacodynamics

PD is the study of the effect of a drug on the body; in particular, the effect of the drug as it relates to increasing dose.

pharmacogenomics

The science of understanding the correlation between an individual patient's genetic make-up (genotype) and their response to drug treatment. Some drugs work well in some patient populations, and not as well in others.

pharmacokinetics

PK is the study of drug absorption, and drug distribution within the body, drug metabolism, and drug excretion.

phosphorylation

Addition of a phosphate (PO_4) group to a molecule, usually enzymatically done by transferring a phosphate group from ATP (adenosine triphosphate).

pI

Isoelectric point, the pH at which a substance has no net charge; above which a substance acts as a base and below which it acts as an acid. A solution of proteins or amino acids has its minimum conductivity and viscosity at the isoelectric point. The pI is a pH value for a given substance; for example, the pI of gelatin is pH 4.7. pI can be used to identify and characterize proteins.

plasmid

Hereditary material that is not part of a chromosome. Plasmids are circular and self-replicating and found (naturally in bacteria and some yeasts) in the cytoplasm of cells. They can be used as vectors for introducing up to 10,000 base pairs of foreign DNA into recipient cells.

polishing

The final purification step(s) in a biopharmaceutical manufacturing process, usually involving an affinity or other refined chromatography method. Often, this step is the most expensive technique in the process because it handles the smallest amount of material.

polyclonal antibody

A mixture of antibodies that recognize different epitopes on the same antigen; each antibody is produced by a different B-cell.

post-translational modification

After a DNA sequence has been interpreted, and a protein has been created, it may be modified by the addition of sugar (glycosylation) or other molecules. This protein processing is done by the Golgi bodies after proteins have been constructed by ribosomes.

preclinical studies

The testing of experimental drugs in the test tube or in animals. The testing that occurs before trials in humans may be done.

protease

An enzyme that cleaves the peptide bonds linking amino acids in protein molecules, classified according to the most prominent functional molecular group (such as serine or cysteine) at the active site; also called proteinase.

protein variants

Proteins with the same amino acid sequences but different folds or different carbohydrate residues. They must be separated from the therapeutic proteins.

proteins

Complex organic macromolecules whose structures are coded in an organism's DNA. Each is a chain of more than 40 amino acids in peptide linkages that folds back upon itself in a particular way. Proteins are the principal constituent of all cell protoplasm (the entire contents of a live cell). Each protein has a unique, genetically defined amino acid sequence that determines its specific shape and function (as enzymes, structural elements, hormones, and immunoglobulins, involved in oxygen transport, muscle contraction, or electron transport, for instance).

protein therapeutics

See large molecule drugs.

proteolysis

Separation (cleavage) of peptide bonds in proteins by proteases (enzymes that recognize and cut specific peptide bonds) or other means.

proteome

The entire set of proteins in an organism.

proteomics

The large-scale study of the structure and function of proteins.

Q-R

quality assurance

QA comprises the quality systems and processes used to control every step of pharmaceutical manufacturing to ensure that the product meets all of its specifications and quality attributes, and that all steps were done and documented in compliance with cGMP.

quality control

QC is the system of testing that confirms and measures the quality of raw materials, process intermediates, final product, and environmental samples.

recombinant

Refers to DNA (or the protein resulting from such DNA) that has been genetically engineered to contain genetic material from another organism. Genetically altered microorganisms are usually referred to as recombinant, whereas plants and animals so modified are called transgenic. See transgenics.

redox

Equilibrium reaction of oxidation/reduction, for example, thiol-disulfide exchange, a step used during refolding of recombinant proteins that contain cysteine (Cys) residues, to form correct pairing of sulfhydryl groups (-SH) and form stable disulfide (S-S) bonds.

RNA

Ribonucleic acid, the nucleic acid based on ribose (a sugar) and the nucleotides G, A, U, and C. It translates the information encoded by DNA into amino acid sequences the cell uses to make proteins. Similar to DNA but based on ribose, and with the base uracil (U) in place of thymine (T). Various forms of RNA are found; mRNA (messenger RNA), tRNA (transfer RNA), and rRNA (ribosomal RNA). Most RNA molecules are single-stranded, although they can form double-stranded units.

S

secondary structure

In proteins, the folding, twisting, coiled, sometimes spring-like chain that results when hydrogen bonds form between the adjacent parts of a molecule, as in an *alpha* helix or *beta* sheet.

small molecule drug

A drug that is chemically synthesized in the laboratory. Small molecule drugs are small enough to enter cells.

SOPs

Standard operating procedures; detailed (step-by-step), instructions to achieve uniformity in the performance of a specific process or piece of equipment, which are approved by the quality control unit and used for GMP operations.

T-U

tertiary structure

The three-dimensional folding (its normal state) of a polypeptide chain in a protein molecule.

transgenics

The alteration of plant or animal DNA so that it contains a gene from another organism. There are two types of cells in animals and plants, germ-line cells (the sperm and egg in animals, pollen and ovule in plants) and somatic cells (all other cells). Germ-line DNA is altered in transgenic animals and plants so those alterations are passed on to offspring. That is done to produce therapeutics, to study disease, and to improve livestock strains. Transgenic plants have been created for increased resistance to disease and insects as well as to make biopharmaceuticals.

translation

The process by which information transferred from DNA by RNA specifies the sequence of amino acids in a polypeptide (protein) chain.

tRNA

Transfer RNA, a type of RNA with triplet nucleotide sequences that complement the nucleotide coding sequences of mRNA. In protein synthesis, tRNA bonds with amino acids and transfers them to the ribosomes, where proteins are assembled according to the genetic code carried by mRNA.

unfolding

A form of protein degradation in which the three-dimensional structure of a molecule unravels to something that more closely resembles a basic chain of amino acids.

upstream processing

The phase of biomanufacturing that consists of establishing cell banks and seeding and scaling up cell cultures.

V-Z

vaccines

Preparations that elicit an immune response (production of antibodies) to protect a person or animal from a disease-causing agent.

virus

The simplest form of life: RNA or DNA wrapped in a shell of protein, sometimes with a means of injecting that genetic material into a host organism (infection). Viruses cannot reproduce on their own, but require the aid of a host (bacteria, plant, or animal). The host cell's synthesis is often inhibited by the infecting virus, which may or may not result in disease (more than 200 viruses are known to produce human disease). An individual virus particle is called a virion, and virions vary in structure, complexity, and size (ranging from 20-25 nm or less to 2,000 nm or more). Six classes of virus are defined by whether they are single or double stranded, DNA or RNA, or positive or negative.

well-characterized

A chemical entity whose identity, purity, impurities, potency, and quantity can be determined and controlled; most well-characterized biologics are recombinant DNA-derived proteins or monoclonal antibodies.

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