

[BIOTERMINOLOGY]

A Guide to the Biopharmaceutical Lexicon

2012 edition

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BIOTERMINOLOGY AND DEFINITIONS

A

absorption Removal of a particular molecule from a sample by accumulation into a bound water volume such as might be present in a densely fibrous material. In pharmacology (and more specifically pharmacokinetics), absorption is the movement of a drug into the bloodstream. Absorption involves several phases. First, the drug needs to be introduced via a route of administration (oral, via the skin, etc.) and in a specific dosage form such as a tablet, capsule, and so on. (See adsorption).

accelerated stability tests Studies in which the product is stored under stress conditions (for example, 45 °C and high humidity over three to six months) and observed for signs of degradation; used to predict long-term storage patterns.

acceptance criteria Numerical limits, ranges, or other suitable measures for accep-

tance of the results of analytical procedures which the drug substance or drug product or materials at other stages of their manufacture should meet. [From ICH Q6B]

ACN *Acetonitrile*; the most frequently used solvent in HPLC, commonly used as an eluent.

acidic variant A product variant that exhibits a more negative charge character by IEX or CE than the primary biotherapeutic form.

active starting material The raw material that is identified as directly related to the active chemical comprising the product, and is defined at the first stage during chemical synthesis at which part or most of the critical moieties are present. Defining active starting material defines the step at which compliance with cGMP requirements begins during manufacturing. For biopharmaceuticals, this term is not used.

acute Describes a disorder as a one-time

Following acronyms that appear in brackets throughout the guide represent the sources of definitions:

- **FDA QSG** definition is the one that appears in the US FDA's Quality Systems guidance.
- **ICH Q6B** definition is the one that appears in the International Conference on Harmonization (ICH) Q6B guideline, "Test Procedures and Acceptance Criteria for Biotechnological/Biological Products."
- **ICH Q8** definition is the one that appears in the ICH Q8 guideline, "Pharmaceutical Development."
- **ICH Q9** definition is the one that appears in the ICH Q9 guideline, "Quality Risk Management."
- **ICH Q11** under review; definition is the one that appears in the ICH Q11 guideline, "Development and Manufacture of Drug Substances (chemical entities and biotechnological/biological entities)."
- **ISO 14971** Refers to the International Organization for Standardization's standard 14971, "Medical Devices—Application of risk management to medical devices."
- **ISO/IEC Guide 51** Refers to the joint ISO and IEC (International Electrotechnical Commission) publication, "Safety aspects—Guidelines for their inclusion in standards."
- **ISO Guide 73** Refers to ISO Guide 73, "Risk management—Vocabulary—Guidelines for their use in standards."

condition (an injury or infection), rather than as a chronic disease such as diabetes.

ADME *Absorption, distribution, metabolism, and excretion.*

adjuvant A chemical agent added to vaccines to boost the immune response to the vaccine antigen.

ADR *Adverse drug reaction*, an undesirable effect that may be caused by a study drug (see also adverse events).

adsorption Adherence of molecules in solution or suspension to cells or other molecules—or to solid surfaces, such as chromatography media. Compare to absorption.

adventitious agents Acquired, accidental contaminants in a cell line, such as viruses and toxins; often infectious agents.

adverse events (see also ADR) Undesired effects or toxicity in a patient due to exposure (often to a drug or medical device, but not limited to those). Adverse events must be notified to the sponsor, who is required to perform a written investigation into the root causes, and may need to take other corrective or preventive actions. (See complaints, CAPA)

aerobic Growing in the presence of oxygen. A strict aerobe grows only under such a condition.

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

affinity chromatography A chromatographic method that makes use of the specific binding of one molecule to another; immunoaffinity chromatography uses antibodies, for example, and metal affinity



One of the most frequently used solvents in chromatographic analysis is ACN, acetonitrile.

chromatography uses chelation.

affinity tag (or tail) An amino acid sequence added to a protein to facilitate purification by affinity chromatography.

agarose A polysaccharide (sugar) obtained from seaweed and used as a solidifying agent (agar) in microbial culture; also used in gel electrophoresis.

aggregate A clustered mass, as of protein molecules; or to cluster together in such a way. Aggregates of cells (solid, fluffy, or pelletized) can clog the pores of filters or other fermentation apparatus.

Ala *Alanine*; one of more than 20 naturally occurring amino acids.

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 protein secondary structure.

amino acid analysis Hydrolysis of a protein or peptide into its individual residues (free amino acids), followed by chromatographic separation and UV-visible detection for analytical purposes.

amino acids A class of 20 naturally occurring hydrocarbon molecules that combine to form proteins in living things. They include alanine (A), arginine (R), asparagine (N), aspartic acid (D), cysteine (C), glutamic acid (E), glutamine (Q), glycine (G), histidine (H), isoleucine (I), leucine (L), lysine (K), methionine (M), phenylalanine (F), proline (P), serine (S), threonine (T), tryptophan (W), tyrosine (Y), and valine (V). (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.

amorphous Having no apparent shape or order; non-crystalline.

ampholyte An electrolyte that can be either positively or negatively charged, depending on the pH of its medium.

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.

ampule A small, sterile glass vessel with an airtight seal that contains a single drug dose.

amyloid Insoluble fibrous protein aggregates sharing specific structural traits. Abnormal accumulation of amyloid in organs may lead to amyloidosis and may play a role in various other neurodegenerative diseases.

anaerobic Growing in the absence of air or oxygen. Some anaerobic organisms are killed by brief exposure to oxygen, whereas it may simply retard or stop the growth of others.

analytical methods Processes used to analyze or characterize a mixture, a compound, or an unknown material.

anion A negatively charged ion (having more electrons than protons).

annual review An evaluation, conducted at least annually, which assesses the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures. [From FDAQSG]

anodes Positive electrodes; negative ions (anions) migrate carrying electric current toward positive anodes.

antibody An infection-fighting protein molecule that tags, neutralizes, and helps

Amino acid analysis can be used to quantitatively determine the amount of protein and the proportions of amino acids in a sample. The Waters UPLC Amino Acid Analysis Solution is a turnkey chromatographic system that provides accurate, high-throughput amino acid analysis.



destroy foreign microorganisms or toxins.

Also known as immunoglobulins, antibodies are produced by the immune system in response to antigens.

antifoam agent A chemical added to a fermentation broth to counteract the foaming (bubbles) that can be caused by mixing, sparging, or stirring.

antigen Any agent that reacts specifically with an antibody. Each antigen may 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.

antisense oligonucleotides Antisense oligonucleotides interact with complementary strands of nucleic acids, modifying expression of genes.

API *Active pharmaceutical ingredient*; the chemical entity that has the drug activity and structure, but is not yet formulated with excipients.

aprotinin A polypeptide that inhibits (blocks the action of) serine proteases.

aptamer Single-stranded RNA or double-stranded DNA molecules made up of short lengths of nucleic acids that form three-dimensional structures and can bind to specific endogenous targets to produce its biological action.

aqueous solution A solvent solution made with water.

Arg *Arginine*; one of more than 20 naturally occurring amino acids.

artificial chromosome DNA synthesized in chromosomal form for use as an expres-

sion vector.

aseptic Sterile, free from bacteria, viruses, and other pathogenic contaminants.

Asn *Asparagine*; one of more than 20 naturally occurring amino acids.

Asp *Aspartic acid*; one of more than 20 naturally occurring amino acids.

assay A technique (test) for measuring a biological response or for determining characteristics such as composition, purity, activity, and weight.

ATD *Arrival time distribution*; mobility-separated ions show a spread of arrival times at the detector, dependent on their shape. The distribution of these arrival times can be used to determine the differences in shape.

ATP *Adenosine 5'-triphosphate*; helps cells conserve and spend energy and often is used in assays of various ATP-dependent enzymes.

attenuated Weakened (attenuated) viruses can be used as vaccines; they can no longer produce disease but still stimulate a strong immune response similar to the natural virus. Examples include oral polio, measles, mumps, and rubella vaccines.

AutoBlend In chromatography systems manufactured by Waters, AutoBlend mode allows the automatic blending of up to four buffers, salts, or solvents in accurate proportions reproducibly, which can simplify mobile phase preparation. Any sequence of isocratic, binary, ternary, and quaternary gradients (very useful for SEC) can be used. The technique is useful for routine assays as well as automatic method development or system flushing.

AutoBlend Plus AutoBlend Plus

technology extends the capabilities of AutoBlend by automatically managing pH and ionic strength requirements for the mobile phase. The software calculates the proportions of buffer stocks required for desired conditions. Computation can be based on known pK values or on an empirical calibration table, making any possible buffer combination available.

autoradiography A technique that uses X-ray film to visualize radioactively labeled molecules or molecular fragments; used in analyzing the length and number of DNA fragments after separation by gel electrophoresis.

B

Bacillus subtilis A Gram-positive, aerobic, endospore-forming, rod-shaped bacterium commonly found in soil, bodies of water, sewers, and in association with some green plants; the second most common species used in recombinant fermentation; also known for its ability to handle organic waste in other types of biotechnology such as bioremediation.

bacteriophage A virus that infects bacteria, sometimes used as a vector.

bacteriostatic agent A chemical agent that prevents microbes from multiplying but does not reliably kill them. May be used during processing, in raw materials, or in final products, especially multiple dosage medicines.

baculovirus A virus that replicates only in the cells of Lepidopteran insects; it has been genetically engineered to force the insect cells in culture to produce large

amounts of a given protein through its natural method of replication, that is, injecting DNA into each cell.

baseline Observations or data used for comparison or as a control.

base pair Two bases on different strands of nucleic acid that join together. In DNA, cytosine (C) always pairs with guanine (G) and adenine (A) always links to thymine (T). In RNA molecules, adenine joins to uracil (U).

basic variant A product variant that exhibits a more positive charge character by IEX or CE than the primary biotherapeutic form.

batch A quantity of a drug substance or drug product with uniform character and quality, within specified limits, produced according to a single manufacturing run during the same cycle of manufacture.

batch culture Large-scale cell culture in which cell inoculum is cultured to a maximum density in a tank or airlift fermentor, harvested, and processed as a batch.

benchtop A term used to distinguish between laboratory-scale or small-scale processes, those that can be performed “on the bench” (in the lab or even on a tabletop) and larger, pilot- or production-scale processes. Benchtop equipment (a “benchtop bioreactor,” for example) can fit on a table or in a confined laboratory area.

beta sheet (β -sheet) A structure resulting from the regular, accordion-like folding of polypeptide chains; the chief alternative to the alpha helix.

BEVS *Baculovirus expression vector system*; an insect cell culture method in which a genetically engineered virus transfers recombinant DNA to the insect cells it infects,



Biopharmaceutical development, manufacturing, and analytical methods use a variety of buffer solutions.

which then produce the peptide or protein in large quantities.

BFS *Blow-fill-seal*; a type of fill-and-finish system used in the pharmaceutical industry that forms a plastic container, fills that container, and then seals it with in-line machinery.

BHK *Baby hamster kidney cells*; an established mammalian cell line that is commonly used for biotechnology.

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

bioanalytical Sub-discipline of analytical chemistry covering the quantitative measurement of xenobiotics (drugs and their metabolites, and biological molecules in unnatural locations or concentrations) and biotics (macromolecules, proteins, DNA, large molecule drugs, metabolites) in biological systems.

bioassay Inoculation of an infective substance into an animal to see if it develops the same disease as a control animal; other analytical methods that use living cells, tissues, or organisms as test subjects.

bioavailability Describes the fraction of an administered dose of unchanged drug

that reaches systemic circulation, one of the principal pharmacokinetic properties of drugs.

biobetter A term for a follow-on biologic that implies some improvement on an existing biologic. This, and similar terms, are not generally used by regulatory authorities. (See biosimilar)

bioburden The number of contaminating microbes (bacteria, yeast, mold, etc.) on or in a certain amount of material before that material has been sterilized.

bioburden assay Microbiological test that enumerates microbial content of a sample, but that is not validated to determine sterility.

bioequivalency "The absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study," Center for Drug Evaluation and Research (2003), *Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations* .

biogeneric A term used for a biopharmaceutical product that is produced and licensed by a different firm than the one that originally licensed the molecule. 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.

bioinformatics Use of computers in the life sciences: for instance, searching and

analysis of electronic databases of genomes and protein sequences, and computer modeling of biomolecules and biologic systems.

biological activity The specific ability or capacity of a product to achieve a defined biological effect. Potency is the quantitative measure of biological activity. [From ICH Q6B]

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

Biologics Price Competition and Innovation (BPCI) Act In 2009, the US Congress passed the Biologics Price Competition and Innovation (BPCI) Act, authorizing FDA to oversee an abbreviated pathway for approval of biologics that are biosimilar to already approved products.

biomarker In either small or large molecules, the presence or absence of an enzyme, receptor, other protein or peptide, a mutated mRNA, or a genetic mutation, that differentiates patient subpopulations and is indicative of a disease, the disease severity, a stage in a disease, a subpopulation with the disease that are differentiated by their drug response, or a subpopulation of people with a different drug activity or pharmacokinetics.

biomass The dry weight estimation of organisms (usually microorganisms) in a given habitat or medium.

biometabolism Physical and chemical processes that occur within a cell or an organism—the conversion of nutrients into energy, for example.

biopharmaceutical A therapeutic product created through the genetic manipulation of living things, including (but

not limited to) proteins and monoclonal antibodies, peptides, and other molecules that are not chemically synthesized, along with gene therapies, cell therapies, and engineered tissues.

BiopharmaLynx™ Application Manager for MassLynx™ Software; Software available from Waters Corporation that automates the data analysis and reporting of mass spectrometry data for peptide maps and intact mass measurements. It automatically analyzes and assigns results, defining the sequence/features of known proteins, and determining the ID of modified forms. Allows users to edit assignments, annotate new peaks, and compare experimental samples to a reference by using tabular and graphical visualization tools.

bioprocessing Using organisms or biologically derived macromolecules to carry out enzymatic reactions or to manufacture products.

bioreactor A vessel capable of supporting a cell culture in which a biological transformation takes place (also called a fermenter or reactor).

biosimilar A biopharmaceutical that is produced using a different cell line or master cell bank and/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, follow-on biological)

biotechnology The industrial use of living things, specifically genetically engineered organisms.

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.

blinding Clinical trial technique in which, to eliminate bias in a research study, subjects (and sometimes clinical investigators) remain unaware of which therapeutic approach (for example, investigational product or standard treatment) is provided.

Blood-brain barrier To protect the brain from infection and from damage that could be caused by foreign chemicals, the endothelial cell linings of its capillaries are tightly packed together. Nothing but water and nutrients that are actively transported by cellular mechanisms can pass through.

blotting Transfer of nucleic acids or proteins from an electrophoresis gel strip to a chemically reactive paper or membrane (such as nitrocellulose paper) or matrix (nylon, for example)—to which they bind. Blotting is achieved through capillary diffusion (when the gel is placed between the paper or matrix and an absorptive pad) or through electrophoresis (electroblotting). Of the three types of blots, Southern hybridization (or Southern blot) transfers DNA; Northern blots transfer RNA, and Western blots transfer proteins (also called protein blots).

bolus A concentrated mass of injected medication.

bond A mechanism through which atoms, ions, or groups of atoms are held together in a molecule.

broth The contents of a microbial bioreactor: cells, nutrients, waste, and so on.

BSA *Bovine serum albumin*; a protein derived from cow serum and commonly used as a growth additive for animal cell culture.

BSE *Bovine spongiform encephalopathy*; the TSE of cattle believed capable of crossing the species barrier to have become feline spongiform encephalopathy (FSE) in cats, transmissible mink encephalopathy (TME) in farmed mink, and vCJD in human beings.

buccal delivery Transmucosal (across the mucosal membranes) drug delivery by way of the mouth.

buffer (buffering agent) A solution containing a weak acid and a conjugate base of this acid; it resists change in pH near a specific value when an acid or a base is added to it because the acid neutralizes any added base and vice versa. For example, bicarbonates and some proteins in biological fluids, when in solution, tend to stabilize the hydrogen-ion concentration by neutralizing (within limits) both acids and bases so the solution resists changes in pH.

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.

bulking agent An additive that increases the volume of a solution or a solid.

C

cake The solid sediment that has been compacted in a centrifuge after removal of as much liquid as possible; or the remaining solid after completion of a lyophilization.

calorimetry Analytical method that measures heat loss or gain resulting from physical or chemical changes in a sample. Differential scanning calorimetry compares the results of heating a sample to those for heating a reference material—for example, to measure the temperature at which the sample crystallizes, changes phase, or decomposes.

campaign production Continuous production of successive batches of the same product.

CAPA *Corrective and preventive action*; a quality system defined by 21CFR 820.100; the policies, procedures, and support systems that enable a firm to assure that exceptions are followed up with appropriate actions to correct the situation, and with continuous improvement tasks to prevent recurrence and eliminate the cause of potential nonconforming product and other quality problems.

[From FDAQSG]

capillary electrophoresis The miniaturized instrumental version of traditional electrophoresis using capillary column technology (that is, tiny fused-silica tubes with 20 to 100 μm inner diameters) and light-absorbance or fluorescence detection.

capsid The outer protein shell of a virus particle (virion).

carbohydrates Molecules consisting of sugars. The basic carbohydrate units are called monosaccharides, such as glucose, galactose, and fructose. Monosaccharides can be linked together into what are called polysaccharides (or oligosaccharides) in almost limitless ways. Oligosaccharides contain a small number (typically three to 10) of component sugars.

carbonyl bond An oxygen atom double-

bonded to a carbon atom; the carbon atom then has two additional bonds to attach to the rest of the molecule.

carcinogenic Cancer-causing; many agents that are carcinogenic are mutagens (agents that increase the occurrence of mutation).

cascade effects A series of events that result from one initial cause.

catabolites Waste products of catabolism, by which organisms convert substances into excreted compounds.

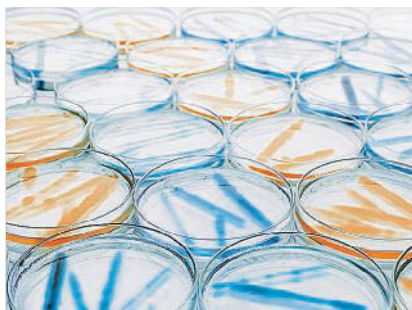
cation A positively charged ion (having fewer electrons than protons).

CBE *Changes being effected*; a regulatory submission sent to FDA to notify them of minor changes in a manufacturing process or its control. The sponsor is permitted to make the changes without waiting for FDA response, and the changes become part of the existing licensed process. (See PAS)

CBE-30 *Changes being effected within 30 days*; a regulatory submission sent to FDA to request minor changes in a manufacturing process or its control. FDA has 30 days in which to respond, after which the change is considered approved and the part of the existing licensed process. (See PAS)

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

CCD *Charge-coupled device*; semiconductors connected so that the output of one serves as the input for the next (digital cameras, video cameras, and optical scanners all use CCD arrays); a light-sensitive integrated



Cell culture on the smallest scale uses petri dishes.

circuit that stores and displays the data for an image.

CCS *Rotationally average collision cross-section*; The CCS of an ion is used to calculate the area of an ion in the gas phase and expressed in Omega (see also Omega). Omega can be calculated empirically through the measurement of an ion's drift time as it passes through a gas filled drift tube or travelling wave ion guide (see also TWIG).

CD *Circular dichroism*; the absorption of left and right circularly polarized light, a property of molecules that are optically active. CD spectroscopy is a form of light-absorption spectroscopy that measures the difference in left and right circularly polarized light absorbed by a substance. The spectra can be analyzed to learn the different secondary structural types in a protein: alpha helix, parallel and antiparallel beta sheet, turn, and so on.

CDC *Centers for Disease Control and Prevention (Atlanta, GA)*; an agency of the Department of Health and Human Services. CDC develops and applies disease prevention and control, promotes environmental health, and provides health education.

CDER *Center for Drug Evaluation and Research*; the largest of FDA's six centers, CDER regulates prescription and over-the-counter drugs. Following a transfer of responsibility for biologics that began in June 2003, CDER now also regulates therapeutic proteins and monoclonal antibodies for *in vivo* use, which were formerly regulated by CBER.

CE *Capillary zone electrophoresis*; an analytical method in which a mixture is fractionated using charge; analytes are detected using optical density, mass, or other physical properties. Also called CZE.

cell bank A defined population of cells, such as an immortalized cell line, grown by a defined process and cryopreserved in a defined process and within a defined passage number range. The assumption is that each vial from a cell bank is comparable, and when thawed and added to a manufacturing vessel (or an analytical assay), will perform in a consistent way. (See master cell bank, working cell bank)

cell banking Developing, reproducing, aliquoting, and storing cells at a defined passage and homogeneity for particular uses.

cell culture Cells taken from a living organism and grown in the lab (in "culture"). Methods used to grow animal cells in the lab are usually different from those used to grow microorganisms such as bacteria.

cell lines When cells from the first culture (taken from the organism) are used to make subsequent cultures, a cell line is established. Thanks to genetic or other manipulations, immortal cell lines can replicate indefinitely.

cellulose A fibrous polysaccharide material, the main ingredient of plant cell walls.

centrifugation Spinning samples at high speeds, using centrifugal force (up to 500,000 times the force of gravity) to separate substances with very small differences in density or weight.

centrifuge A laboratory or industrial apparatus that separates mixed samples of differing density by spinning them at high speed.

certificate of analysis (COA) A batch-specific document that is used to list test methods and results, including applicable specifications, and a final batch disposition

CFR *Code of Federal Regulations*; the US regulations that directly apply to biopharmaceutical development are in Title 21 parts 58, 210, 211, and 600. Parts 50, 56, and 312 apply to clinical trials.

cfu *Colony forming units*; a measurement of the number of microorganisms present derived from the number of colonies that form in a test culture.

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 the water, molecules, or systems.

characterization Precisely deciphering and describing an entity's properties (physical and chemical properties in the case

of a molecular entity; genetic and stability properties in the case of a cell line).

charge The electrical state of an atom or molecule, whether positive, negative, or neutral, according to the difference of protons (positively charged) to electrons (negatively charged).

chelation The binding or holding of a metal ion (such as copper, zinc, cadmium, nickel, or cobalt) by another molecule or by another part of the same molecule; used in a form of affinity chromatography called "metal chelate chromatography."

chelator A molecule used to bind a metal ion with more than one organic group to form a highly stable structure.

chemical synthesis A non-biotech method of manufacturing chemicals, including drugs.

chemostat A growth chamber that keeps a bacterial culture at a specific volume and rate of growth by limiting nutrient medium and removing spent culture.

chimera Chimeric proteins (or fusion proteins) are created through the joining of two or more genes that originally coded for separate proteins.

chirality The condition of being chiral, that is, a molecule in a configuration that is symmetrical with its mirror image; a right-handed chiral molecule rotates polarized light rightward, a left-handed chiral molecule rotates polarized light leftward.

CHO cells *Chinese hamster ovary cells*; in cell culture, the cells of a female hamster's reproductive organs, which historically have proven to be the basis for good expression systems in analytical studies and for producing pharmaceutical proteins.

chromatography A technique used to separate molecules based on how they tend to bind to various solids, liquids, and gases; based on the differential distribution of the substances between a stationary phase (sticky material such as silica gel or silicic acid, usually contained in a column, tube, or capillary) and a gaseous or liquid mobile phase (a medium that carries the sample through the stationary phase). This very effective technique can separate substances that are nearly identical.

chromophore A molecule that absorbs UV or visible light.

chromosome A long and complex DNA chain containing the genetic information (genes) of a cell. Prokaryotes contain only a single chromosome; eukaryotes have more than one, made up of a complex of DNA, RNA, and protein. The exact number of chromosomes is species-specific. Humans have 23 pairs.

chymotrypsin A digestive enzyme that can cleave peptide bonds.

CIP *Clean-in-place*; a way to clean large vessels (tanks, piping, and associated equipment) without moving them or taking them apart, using a high-pressure rinsing treatment, sometimes followed by steam-in-place (SIP) sanitization. Chemically cleaning and sterilizing equipment or systems without removing them from their installed location.

clarify To clear liquid of suspended particles through filtration, extraction/precipitation, or centrifugation.

classical pharmaceuticals Small-molecule, non-biotech drugs produced by chemical synthesis.

clean room A room in which the con-

centration of airborne particulate matter is controlled at specific limits to facilitate the manufacture of sterile and high-purity products. Clean rooms are classified according to the number of particles per volume of air to meet standards of cleanliness. Contaminants on surfaces and people entering and exiting the room also are controlled.

clearance Clearance—in volume/unit time—of a drug or chemical from a body fluid, usually plasma or blood, by specified route(s) and mechanism(s) of elimination, as indicated by a subscript (e.g., Cl_R , urinary clearance; Cl_H , hepatic clearance, etc.). Cl_T , total clearance, indicates clearance by all routes and mechanisms of biotransformation and excretion, operating simultaneously. $Cl_T = k_{el} \cdot V_d$. Following intravenous administration, $Cl_T = D/AUC$; following administration of drug by any route other than the intravenous, $Cl_T = F D/AUC$.

clinical development The phases of drug development during which a drug is tested in human subjects, also referred to as clinical trials.

clinical endpoint An indicator (such as blood pressure) measured in a human subject to assess the safety, efficacy, or other objective of a clinical trial.

clinical hold Temporary cessation of a clinical trial by FDA if the agency is concerned about a drug or study protocol. The trial may resume when the problem is solved.

clone To duplicate exactly, whether a gene or a whole organism; or an organism that is a genetically identical copy of another organism.

cloning vectors Methods of transferring

desired genes to organisms that will be used to express them. Cloning vectors are used to make recombinant organisms.

CM *Carboxymethylcellulose*; a weak ion-exchanger that is often coupled to a resin used in charge based separation chromatography. It is a cation exchange resin.

CMC *Chemistry, manufacturing, and controls*; the section of a BLA, NDA, or IND describing the composition, manufacture, and specifications of a drug product and its ingredients.

CMO *Contract manufacturing organization*; a company contracted to perform development and/or manufacturing services.

codon A sequence of three nucleotide bases in mRNA that specifies production of an amino acid or represents a signal to stop or start a function.

colorimetry The measurement and definition of unknown colors in terms of standard colors; techniques may be visual, photoelectric, or spectrophotometric; colorimetry is useful in determining the concentration of a chemical with color in a solution by measuring the intensity of the color and relating that intensity to the concentration of the solution.

column A vertical, cylindrical container or vessel often used in separation processes such as extraction, distillation, and chromatography.

column aspect ratio The ratio of a column's height to its diameter.

column chromatography A separation method in which the different components of a mixture migrate through a column at different rates of speed based on their relative affinity for the stationary phase.

comparable Product made before and after a given process change is comparable if the change is shown to have no adverse effect on the key quality attributes of the product, such as purity, potency, PK/PD, stability, and safety. Small differences in, for example, the impurity profile are permitted, as long as the function is not affected. (See equivalent)

comparability protocol A protocol that defines the experiments and acceptance criteria that will be used to evaluate a product before and after a process change, and if met, will provide documented evidence that the products are comparable.

complaint Also customer complaint; any oral or written communication from an end user of a medicinal product indicating that it had an adverse effect on a patient, did not function as specified, or appeared to be contaminated or defective in any way. The sponsor must promptly investigate all such complaints and document the investigation in a retrievable file. If the complaint is confirmed, corrective and preventive actions are required. Examples include FDA notification, product lot(s) withdrawal, product recall, and review of medical files of adverse events caused by the product. These requirements are found in US regulations in 21 *CFR* 314, the GCP regulations.

complement A group of proteins in the blood that work in concert with other immune system proteins and cells (such as antibodies) in attacking foreign substances.

component 1. Raw materials and components (tubing, stoppers, vials, filters) having direct product contact during manufacturing, which are regulated under 21 *CFR* 84.

2. Differentiated from raw materials and excipients, which are chemical entities, and usually rated as lower in risk to patient and product quality. (Note: These terms may be used interchangeably or loosely, and definitions vary between US, Europe, and WHO). (See raw material, starting material, API)

concentration The amount of a particular substance in a given quantity of solution, usually stated as a percentage by weight or volume, as weight per unit volume, as molarity (a one-molar solution contains one gram-mole of solute per liter of solution), or as normality (a one-normal or one-molar solution contains one gram-equivalent weight of solute per liter of solution).

conformation The shape of a molecule, produced by the specific spatial arrangement of the units that compose it.

consent decree Status imposed by FDA on a company in serious violation of federal regulations and related safety and quality standards. A company must agree to a series of measures aimed at bringing its manufacturing standards into compliance with federal regulations. Until agreed-upon conditions are met, a company may be for-



Columns for bioseparations are available in a wide variety of dimensions, chemistries, and pore sizes to best meet separation requirements.

bidden to distribute its products in interstate commerce, except for those products deemed essential for the public health.

contaminant A foreign agent or material that is not introduced as part of processing, such as airborne particulates or adventitious organisms.

continuous process verification An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated. [From ICH Q8]

control group The group of subjects in a controlled study that receives no treatment, a standard treatment, or a placebo.

controlled delivery Drug delivery in which the duration (sustained delivery) and/or the site (targeted delivery) of drug release, action, and bioavailability are controlled through various physicochemical means designed to provide well-defined pharmacokinetic profiles.

Coomassie blue dye A sensitive stain for proteins used to visualize the bands in SDS-PAGE; also Coomassie brilliant blue.

COS, CV-1 African green monkey kidney cells, an established cell line that is commonly used for biotechnology.

cosmid An artificially constructed plasmid vector that contains a specific bacteriophage gene, which allows it to carry up to 45,000 base pairs of desired DNA.

cot1/2 DNA A curve that measures genome complexity by determining the time taken for half the DNA in a sample to reanneal (renature); it is measured for any new genome and compared to a standard such as the *E. coli* genome.

covalent bond Chemical bond in which

two atoms share one or more electron(s).

Cp *Process capability*; a statistical measurement of the relation between the observed variability of a process and the specifications or requirements for individual lots. Computed by dividing the range by the process variability (sigma); a larger number indicates a more capable process.

critical micellar concentration (CMC)

The concentration of detergent at which micelles begin to form; from a practical point of view, the CMC defines the minimum concentration of free detergent that must be present to keep membrane proteins in solution. CMC values are affected by temperature, ionic strength, pH, and buffer composition. The CMC is important in determining whether a detergent can be removed by dialysis. For example, a free detergent molecule may pass through the membrane but the largest micelle will not. (Compare to CMC: chemistry, manufacturing, and controls.)

critical process parameter An input parameter (process setpoint) to a unit operation that must be tightly controlled by the operator, either manually or automatically, and which must be kept within a specified range in order to produce output of acceptable quality within specifications. These parameters are identified during process development.

critical quality attribute A quality characteristic that must be controlled within defined limits to ensure acceptable product quality and performance.

CRO *Contract research organization or clinical research organization*; a company contracted by a sponsor to perform preclinical

or clinical pharmaceutical research.

cryoconcentration When a solution is frozen, water freezes as pure ice crystals. The remaining liquid therefore has a higher solute concentration than the original solution.

cryoaggranulation Use of a stream of liquid nitrogen to quickly create frozen, discrete pellets of a solution such as bulk or final drug formulation.

cryopreservation Maintenance of frozen cells, usually in liquid nitrogen.

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

culture medium A complex mixture of organic and inorganic materials used as a nutrient system for the cultivation of cells.

cuvette A transparent or translucent box-shaped container with precisely measured dimensions for holding liquid samples to be put into a spectrophotometer; also such a container with optical surfaces used to mold samples so that their light-absorbing properties can be measured.

Cys *Cysteine*; one of more than 20 naturally occurring amino acids.

cytokine A protein that acts as a chemical messenger to stimulate cell migration, usually toward where the protein was released. Interleukins, lymphokines, and interferons are the most common.

cytopathic Damaging to cells, causing them to exhibit signs of disease.

cytoplasm The protoplasm of a cell outside the nucleus (inside the nucleus is the nucleoplasm). Protoplasm is a semi-fluid, viscous, translucent mixture of water, proteins, lipids, carbohydrates, and inorganic

salts found in all plant and animal cells.

cytostat Something that retards cellular activity and production. This can refer to cytostatic agents or to machinery, such as those that would freeze cells.

cytotoxic Causing cell death.

D

Da *Dalton*; the unit of molecular mass, very nearly equal to that of a hydrogen atom (precisely equal to 1 on the atomic mass scale), named after John Dalton, who developed the atomic theory of matter (kDa, kilodalton).

DEAE *Diethylaminoethyl*; a weak ion-exchanger that is often coupled to a resin and used in charge based separation chromatography. It is an anion exchange resin.

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.

Declaration of Helsinki A set of recommendations or basic principles guiding medical doctors in the conduct of biomedical research involving human subjects.

deflashing The finishing procedure by which excess plastic (flash) is removed from a molding in BFS operations.

degradants The smaller parts that are left over after a molecule or solution degrades.

degradation Loss or reduction of quality, integrity, or character; a chemical reaction that breaks down a molecule into smaller parts.

delaminate To split apart into thin layers; the act of separating a laminate into layers.

delivery matrix A heterogeneous semisolid matrix (such as a biopolymer gel) for the sustained delivery of drug substances directly to the tissues; a matrix can be modified to optimize the dosage or time period during which the drug is delivered.

denaturation A condition in which a protein unfolds or its polypeptide chains are disordered, rendering the molecule 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).

derivatization A sampling technique; chemical conversion into a derivative form for identification purposes.

design space The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post-approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval. [From ICH Q8]

desorption The opposite of adsorption; the release of adsorbed molecules, particles, or cells into the surrounding medium.

detergents Cleaning agents: chemicals with both hydrophobic (averse to water) and hydrophilic (water-attracted) properties that can dissolve fats and oils.

dialysis/diafiltration Membrane ultrafiltration in which a large solute (such as a protein) is washed or dialyzed with another solution; for example, changing buffer conditions without affecting protein concentration.

diastereomer A stereoisomer (one of two or more molecules with the same atoms in the same order but different three-dimensional shapes) having two or more chiral centers that is not a mirror image of another stereoisomer of the same compound; glucose, galactose, and mannose are all diastereomers.

differential scanning calorimetry Analytical method that independently measures the rate of heat flow to a sample against a reference standard of the same temperature. Data are obtained by monitoring the differential heat flow as a function of temperature. DSC can measure heat capacities, phase transitions, dehydration, and heats of reaction.

diluent A chemically inert substance added to a solution to increase the volume and reduce the concentration; a diluting agent.

dimer A polymer made up of two identical molecules. When three monomers 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.

dissociation constant A specific type of equilibrium constant that measures the propensity of a larger object to separate (dissociate) reversibly into smaller components, as when a complex falls apart into its component molecules, or when a salt splits up into its component ions. The dissociation constant is usually denoted K_d and is the inverse of the affinity constant. Dissociation constants are commonly used to describe how tightly a ligand (such as a drug) binds to a protein. Such binding is usually non-covalent, i.e., no chemical bonds are made or broken. Since the binding is usually described by a two-state process $P + L = C$ the corresponding dissociation constant is defined $K_d = [P][L]/[C]$ where $[P]$, $[L]$, and $[C]$ represent the concentrations of the protein, ligand, and bound complex, respectively. The dissociation constant has the units of molar (M), and corresponds to the concentration of ligand $[L]$ at which the binding site on the protein is half occupied, i.e., when the concentration of protein with ligand bound $[C]$ equals the concentration of protein with no ligand bound $[P]$. The smaller the dissociation constant, the more tightly bound the ligand is; for example, a ligand with a nanomolar (nM) dissociation constant binds more tightly than a ligand with a micromolar (mM) dissociation constant.

disulfide bond A covalent bond formed between sulfur atoms of different cysteines in a protein; such bonds (links, bridges) contribute to the tertiary structure of the protein.

divalent cations Cations with a net positive charge of +2.

DIW *Deionized water*; very pure water in



This is a simplistic model of the DNA structure.

which contaminants have been ionized and removed by special filtration.

DMPK Drug Metabolism and Pharmacokinetics. Determining the DMPK properties of a drug allows the drug developer to understand the safety and efficacy data required for regulatory approval.

DMSO *Dimethyl sulfoxide*; a common cryoprotectant used to cryopreserve cells and tissues.

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, nucleic acids)

DNA array Spots of DNA, oligonucleotide, or cDNA arranged on a solid support such as a glass or silicon “DNA chip” (or microarray), which is used for screening, sequencing, genetic mapping, and so on.

DNA fingerprinting Sequences of nucleic acids in specific areas (loci) on a DNA molecule are polymorphic, meaning that the genes in those locations may differ from person to person. DNA fragments

can be cut from those sequences using restriction enzymes. Fragments from various samples can be analyzed to determine whether they are from the same person. The technique of analyzing restriction fragment length polymorphism (RFLP) is called DNA typing or DNA fingerprinting. It is also now possible to detect polymorphisms consisting of a single nucleotide. These are called single-nucleotide polymorphisms (SNP).

DNase *Deoxyribonuclease*, the enzyme that breaks up and destroys DNA sequences (a protective mechanism in higher organisms).

DNA sequencing Determining the order of nucleotide bases in a DNA molecule.

DNA vaccine A nucleic acid vaccine: Genes coding for specific antigenic proteins are injected to produce those antigens and trigger an immune response.

DOE *Design of experiments*; a term for experiments that are planned and analyzed using statistical design tools. A structured, organized method for determining the relationship between factors affecting a process and the output of that process. [From ICH Q8]

dosage group A group of subjects in a clinical trial receiving the same dosage of a drug being tested.

downstream processing Bioprocessing steps following fermentation and/or cell culture, a sequence of separation and purification activities needed to obtain the required drug product at the necessary level of purity.

DQ *Design qualification*; a documented review of the design, at an appropriate stage of stages in the project, for conformance to operational and regulatory expectations.

drift time The drift time of an ion is a measure of how long it takes to move through a mobility region in a mass spectrometer. For a travelling wave, this is measured in low hundreds of milliseconds (see also TWIG).

drug discovery Methods for identifying new therapeutic molecules. High-throughput techniques include combinatorial chemistry, genomics, and proteomics analysis as the starting point. Low-throughput methods include traditional disease research.

drug product The final dosage form of a pharmaceutical medicine containing drug substance formulated with selected excipients and packaged for the end user.

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

E

EBA *Expanded-bed adsorption*; a chromatography method that uses an upward flow of liquid in a column of suspended, dense chromatography beads to allow passage of crude, unclarified raw materials without clogging the chromatography medium.

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.

efficiency of delivery The relative effectiveness of a drug delivery system.

EHSS *exact hard sphere scattering*; An

ion is modeled by a collection of overlapping hard spheres with radii equal to hard sphere collision distances (see also PA). The orientationally averaged momentum transfer cross section is calculated by determining the scattering angles between the incoming buffer gas atom trajectory and the departing buffer gas atom trajectory.

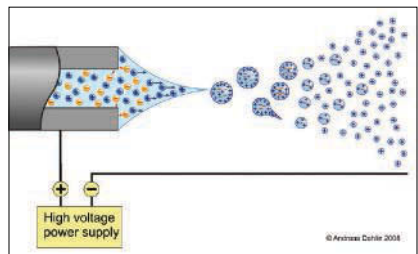
elastomeric closure A rubber or rubber-like closure or stopper; a packaging component that may come into direct contact with the enclosed drug, which is usually an injectable.

electrolytes Ionized salts in body fluids; electrolyte solutions are solutions containing charged atoms or molecules.

electroosmotic The movement of a liquid out of or through a porous material or a biological membrane under the influence of an electric field.

electrophoresis Analytical method in which an electric field is applied to a medium (paper, thin-layer plates, polyacrylamide or agarose gel), causing charged molecules to move through it. In capillary electrophoresis, samples move through a buffer-filled tube (capillary). In gel electrophoresis, samples move through a thin agarose or polyacrylamide gel. Bigger biomolecules (and those carrying few

Electrospray ionization is used to transfer analytes from liquid to a gaseous phase in an ionized form.



electrically charged chemical groups) move slower through the medium than smaller molecules (and those with many electrically charge chemical groups).

electrospray ionization Technique for generation of charged ions for mass spectrometry. Analyte containing solution is dispersed as a fine charged aerosol into the MS by passage of the liquid through a electrically charged capillary emitter.

electrostatic binding A chemical bond of two atoms or molecules by an electrostatic force (like static electricity) caused by one or more electrons moving from one atom to the other.

elimination The rate at which drugs are removed from the body.

ELISA *Enzyme linked immunosorbent assay*; a test to measure the concentration of antigens or antibodies.

eluate Also called elution fractions; the separated components of a mixture that wash out from a chromatography column during elution.

eluent The substance used to recover samples from a chromatography column; sometimes an elution solvent. When a buffering agent is used, it is called an elution buffer. Sometimes a solvent is used and just referred to as the eluent.

elution *Washing out*; removing adsorbed material with a solvent or buffering agent.

elution profile A graph made to show how much material is being carried out of the column by the eluent in column chromatography over time. The graph will show a number of different peaks; each peak represents a different separated material from the original mixed substance. Also called a chromatogram.

elution volume The amount of eluent that passes through the column in column chromatography before a particular peak appears in an elution profile (that is, before a specific substance of interest comes out with it). Also, the volume during which a particular compound is eluted.

EM *Electron microscopy*; in which instruments focus electrons like optical microscopes focus light. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) are sometimes used in bioanalytical laboratories.

EMA *European Medicines Agency*; the agency responsible for regulating biopharmaceuticals in the European Union.

emulsification A process that creates a stable mixture of two liquids that normally would not mix together (such as oil and water) by forcing one to disperse in the other as droplets.

enantiomer Either of a pair of chemical compounds whose molecular structures have a mirror-image relationship to each other (see diastereomer).

encapsidation During formation of a virus particle, the process by which nucleic acid is incorporated (encapsidated) into the viral capsid. (See also capsid)

encapsulation To enclose in a capsule, usually one made of a biodegradable polymer.

endogenous Growing or developing from a cell or organism, or arising from causes within the organism.

endonuclease A restriction enzyme that breaks up nucleic acid molecules at specific sites along their length. Such enzymes are naturally produced by microorganisms as a

defense against foreign nucleic acids.

endoplasmic reticulum A highly specialized and complex network of branching, interconnecting tubules (surrounded by membranes) found in the cytoplasm of most animal and plant cells. The rough endoplasmic reticulum is where ribosomes make proteins. It appears “rough” because it is covered with ribosomes. The smooth endoplasmic reticulum is the site for synthesis and metabolism of lipids, and it is involved in detoxifying chemicals such as drugs and pesticides.

endotoxin A poison in the form of a fat/sugar complex (lipopolysaccharide) that forms a part of the cell wall of some types of bacteria. It is released only when the cell is ruptured and can cause septic shock and tissue damage. Pharmaceuticals are tested routinely for endotoxins.

engineering batch A batch run at the defined cGMP production scale for the purpose of evaluating the performance of any or all of the unit operations prior to initiating cGMP manufacturing. It is not intended to be released as a fully compliant cGMP batch. An engineering batch may be executed using a batch record, but need not comply with all instructions and requirements.

enthalpy Heat content; enthalpy change of a chemical reaction equals the difference between the heat put into breaking bonds and the heat released by new bond formation.

environmental monitoring A documented series of sampling and testing performed on controlled environments to assure compliance with room classifications. Testing typically includes monitoring of

viables and non-viables via standardized sampling methods performed at established time intervals.

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

epithelium (epithelial) The layer(s) of cells between an organism or its tissues or organs and their surrounding environment (skin cells, inner linings of lungs or digestive organs, outer linings of kidneys, and so on).

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.

equivalence Two lots of product are equivalent if, within experimental error, they are essentially equal in purity/impurity, potency, identity, and safety. A more stringent requirement than comparability. (See comparable)

Escherichia coli Bacteria normally found in the intestinal tract and widely used in biochemical and genetic studies and genetic engineering. *E. coli* is often used as a vehicle for combining a segment of DNA with an unrelated segment, creating continuous DNA that does not occur naturally (recombinant DNA).

eukaryotes Complex organisms, often multicellular, whose cells contain nuclei.

exception A deviation from approved GMP procedure; an out-of-specifications result or unexpected or out of trend result; a customer complaint. Exceptions must be detected, investigated, and managed using

quality systems such as CAPA (corrective and preventive action).

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 waters. An excipient must be evaluated for safety in animals, unless it has been approved as GRAS or is on a list of approved excipients.

exclusion limit In size-exclusion (or gel filtration) chromatography, the smallest size or dimension of molecule that is too large to enter the pores on gel particles.

excretion The elimination of substances from the body. In rare cases, some drugs irreversibly accumulate in body tissue.

exogenous Developing from outside, originating externally. Exogenous factors can be external factors such as food and light that affect an organism.

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.

extractables 1. Substances withdrawn

(such as the medicinally active components of plant or animal tissue) by a physical or chemical process. 2. Materials that are actually removed from a container or closure by a given formulation or product. (See leachables)

extraction Liquid-liquid extraction is a process in which a solute is removed from a liquid by transferring the solute into a second liquid phase. The two liquid phases must be insoluble with each other. Separation is based on different solubilities of the solute in the two phases. Extraction is gentle and suitable for unstable molecules.

extrusion A process of forming rods, tubes, or other continuously formed pieces by pushing hot or cold semisoft solid material through a die; also any process of pushing a substance through holes or a tube.

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 inter-chain 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 the intact IgG, which removes the Fc portion of the molecule. F(ab)'₂ binds two moles of antigen per mole. (See Fab)

Fab Antibodies are Y-shaped molecules. The “arms” of each Y are the FAB regions (fragment antigen binding sites) 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.

factors (coagulation factors) Protein constituents of blood, numbered according to the order in which they were discovered, which separate out in a traditional fractionation procedure (Cohn fractionation); Factor VIII, for example, is a blood serum protein involved in clot formation that is also called antihemophilic globulin.

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)

FD&C Act *Food, Drug and Cosmetic Act of 1938*; the major legislation regulating such products in the United States. It requires companies to prove that their products are safe before marketing them, extends FDA oversight to cosmetics and therapeutic devices, explicitly authorizes factory inspections, requires standards for food, and adds injunctions to previous penalties of seizure and criminal prosecution for violations of related laws.

FDA United States Food and Drug

Administration.

FDA-483 A form prepared at the conclusion of an inspection (without review by FDA management) citing observations that may constitute violations of law, in the opinion of the inspector. Originally intended to inform companies of possible product adulteration so that prompt corrective action could be taken, 483s now list a host of observations. Accessible through the Freedom of Information Act by competitors, potential customers, and the media, 483s can lead to withholding of product approvals, may come into play in due diligence phases of acquisitions and mergers, and can potentially cost companies money.

FDAMA *FDA Modernization Act*; enacted in November 1997, this amends the FD&C Act to improve (facilitate) the regulation of food, drugs, devices, and biological products.

feedstock Also feed or feed stream; most often the raw broth containing particles to be removed that is placed into a laboratory or manufacturing appliance such as a centrifuge or chromatography column.

feed stream Also feed or feedstock; most often the solution fed into a reaction or separation/purification process.

fermentation Large-scale cultivation of microorganisms or single-celled creatures for industrial purposes, such as to produce therapeutic molecules or specialty foods and beverages.

fermenter A large bioreactor used to grow bacteria or fungi in liquid culture.

fill-and-finish The part of a manufacturing process concerned with packaging a product in its final form.

filter Porous material through which a liquid or gas is passed so that particulates



Liquid formulations are most common for biopharmaceuticals.

and impurities are held in suspension and removed from the feed stream. Some impurities may pass through.

filtrate The part of a mixture that passes through a filter, also called permeate.

filtration Separation of solid particles from a fluid by passing the mixture through a porous, fibrous, or granular substance.

FISH *Fluorescence in situ hybridization*; an analytical method in which specific sequences of DNA are labeled with fluorescent molecules, hybridized (amplified), and then detected with a fluorescence microscope.

floc A fluffy aggregate that resembles a woolly cloud.

flocculant A precipitate (floc), sometimes a flaky or fluffy aggregate that resembles a woolly cloud; the aggregation (flocculation) of initially separate cells that form flocs.

flux Usually, the rate of flow. A lower flux means slower flow, usually caused by clogging.

fMet *N-formyl methionine*; a variant of the amino acid methionine that many bacterial cells can produce. In mammals, fMet results in a strong adverse reaction by the body.

FMEA *Failure modes evaluation and analysis*; a method used to perform risk assessment and risk mitigation. A unit operation is analyzed, and all the potential modes by which it might fail are mapped out. Then a control strategy is defined to reduce the probability that a given mode of failure will occur. Used in the aerospace and other industries with much success. (See also HACCP)

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 biogeneric.

for-cause inspection An FDA facility inspection carried out because of specific information such as the results of a sample analysis, observations made during previous inspections, product recall or market withdrawal, consumer or employee complaint, adverse reaction report, or suspicion of fraud. Also, a similar inspection of a clinic or an IRB.

forced degradation Also known as accelerated degradation, a process whereby the natural degradation rate of a product or material is increased by the application of an additional stress to rapidly screen material stabilities.

formal experimental design A structured, organized method for determining the relationship between factors affecting a process and the output of that process. Also known as design of experiments. [From ICH Q8]

formamide A colorless, oily, hygro-

scopic liquid used to denature nucleic acids and as a solvent, softener, or chemical intermediate.

formic acid The simplest carboxylic acid, miscible with water and most polar organic solvents, and somewhat soluble in hydrocarbons. It is used in laboratories as a solvent modifier for HPLC separations of proteins and peptides, especially when the sample is being prepared for mass spectrometry analysis.

formulation The method and process of selecting the components of a mixture; the product of such a process; the form in which a drug is given to patients (tablets or injections, for example); developed in concert with a drug delivery system and targeting mechanism needed to get the active ingredient to its site of action.

fraction A separate portion of a mixture, often used to describe the part that contains a particular molecular species.

fractionation range The range of molecular sizes that can fit (or diffuse) into the pores of a gel filtration chromatography medium particle.

free radicals Short-lived, highly reactive molecular fragments that are often capable of initiating/continuing chemical reactions by means of a chain reaction mechanism. They are usually formed by the splitting of molecular bonds, which requires energy input. Free radicals act as initiators or intermediates in oxidation, combustion, polymerization, and photolysis.

FT-IR *Fourier transform infrared spectroscopy*; an analytical method that measures the ability of a sample to absorb different wavelengths of infrared

radiation: How much is absorbed at each wavelength indicates the types of chemical bonds present in the molecules of the sample. The Fourier-transformation is a mathematical method used to interpret the vibrations of functional molecular groups and highly polar bonds. FT-IR produces a “fingerprint” illustrating the vibrational features of all sample components.

functional genomics A method of selecting among the thousands of drug leads that can come out of discovery efforts. Whereas genomics studies the genetic basis of organisms and their diseases, functional genomics challenges drug lead candidates derived from genomic studies with early development-style assays to build as much information as possible about the potential drug into the discovery process.

fusion partner When making a small protein or peptide in *E. coli*, it is often necessary to produce the protein fused to a larger protein to get high levels of stable expression. The resulting fusion protein must be cleaved (chemically or enzymatically) to yield the desired protein or peptide. The non-product fusion partner is left over and usually thrown away.

fusion protein A protein containing amino acid sequences from each of two distinct proteins. It is formed by expression of a recombinant gene in which two coding sequences have been joined together. Typically, this is accomplished by cloning a cDNA into an expression vector in frame with an existing gene.

G

gas chromatography Analytical method in which a volatile substance to be separated is introduced into a stream of nonreactive gas or other stationary phase. For example, in capillary gas chromatography, the gas mixture moves through a tube coated with liquid, and how fast it moves through the tube depends on the degree to which it stays in the nonreactive gas or dissolves in the liquid (partitioning).

GCP *Good clinical practice*; according to 21 *CFR* Parts 56, 312, and 314, the regulations that govern the actions and environment of those working in clinical testing of drugs and medical devices on human beings. These regulations include rules for obtaining informed consent and data integrity requirements.

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. In its infancy, 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-line

gene therapy, the parents' egg and sperm cells are changed with the goal of passing on the changes to their offspring.

genetic engineering Altering the genetic structure of an organism (adding foreign genes, removing native genes, or both) through technological means rather than traditional breeding.

genetic polymorphisms Gene alterations, additions, omissions, or deletions that alter biologic functioning or changes in drug metabolism.

genome The collection of all the genes for an organism.

genomics Study of the genetic make-up of organisms, including sequencing and mapping of their DNA. The Human Genome Project was a government-coordinated effort of many genomics researchers who sequenced and mapped the entire human genome.

genotoxicity Ability of a substance to damage the genome.

genotoxin A substance that causes damage to an organism's DNA.

genotype The genetic composition of an organism (including expressed and non-expressed genes), which may not be readily apparent. Compare to phenotype, the outward characteristics that result from gene expression.

germ cell The "sex cells" in higher animals and plants that carry only half of the organism's genetic material and can combine to develop into offspring.

glass state The amorphous solid that, for example, contains the therapeutic protein in lyophilization; any material that takes the shape of its container and is formed

by cooling a liquid until it is rigid but not crystallized.

Gln *Glutamine*; one of more than 20 naturally occurring amino acids.

GLP *Good laboratory practices*; according to 21 *CFR* Part 58, regulations to ensure quality of nonclinical laboratory studies related to safety. All activity is recorded, trained staff uses only established procedures, and records and samples are maintained.

Glu *Glutamic acid*; one of more than 20 naturally occurring amino acids.

glucose A monosaccharide (or simple sugar) is an important carbohydrate in biology. The living cell uses it as a source of energy and metabolic intermediate.

Gly *Glycine*; one of more than 20 naturally occurring amino acids.

glycan Refers to a polysaccharide or oligosaccharide that can be found attached to proteins as in glycoproteins and proteoglycans.

glycoproteins Proteins that contain sugar side chains added as a posttranslational 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.

GMPS *Good manufacturing practices*; 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,



GLPs provide guidance on the best practices for laboratory activities, from research techniques to records and documentation.

equipment must be qualified, and properly trained staff must maintain a clean/sterile environment.

Golgi body A cell organelle consisting of stacked membranes where posttranslational modifications of proteins are performed; also called Golgi apparatus.

Gram's stain/Gram's method A method developed by Hans C.J. Gram for identifying bacteria. Bacteria are stained with gentian violet, then treated with Gram's solution (water, potassium iodide, and water) and counterstained. They are then treated with alcohol and washed with water. Gram-negative bacteria do not retain the purple dye (*E. coli*, for example); Gram-positive bacteria do retain the purple dye (*Staphylococcus aureus*, for example).

GRAS *Generally recognized as safe*; a special status afforded by FDA to ingredients and methods that have a proven, longstanding history of causing no harm to humans or animals.

growth hormone A protein produced in the pituitary gland to control cell growth.

Guidance for Industry The next regula-

tory level up from a Points to Consider (PTC) document (and below official Code of Federal Regulations law).

GXP All-inclusive term for GCPs, GLPs, and GMPs.

H

HACCP *Hazard analysis and critical control points analysis*; a method used to perform risk assessment and risk mitigation. Each unit operation is evaluated to define what critical parameters must be kept within specified ranges, and the process control strategy is designed to monitor and control within that range. Used in the food industry with much success. (See also FMEA)

half-life ($t_{1/2}$) Time required to decrease the amount of drug in body by 1/2 during elimination (or during a constant infusion).

hapten A small, separable part of an antigen that reacts specifically with an antibody but is incapable of stimulating antibody production except in combination with a carrier protein molecule.

harm Physical injury or damage to the health of people, or damage to property or the environment. [From ISO 14971; see also ICH Q9]

hazard The potential source of harm [From ICH Q9; see also ISO/IEC Guide 51].

HICIC *Hydrophobic charge induction chromatography*; a type of HIC that is based on pH rather than salt concentration, allowing for elution under relatively mild conditions and eliminating the requirement for an associated filtration step in early separations.

HDMS™ (IMS-TOF MS) System *High Definition Mass Spectrometry™ (HDMS)*;

Waters MS Technology that couples high-efficiency ion mobility separations (IMS) with time-of-flight (TOF) mass analysis. HDMS provides an additional dimension of information for separations, providing additional details on glycopeptide, protein, and polymers such as PEG that are conjugated to proteins, including determining partial sequence information of proteins, and differentiating by size and shape, as well as mass.

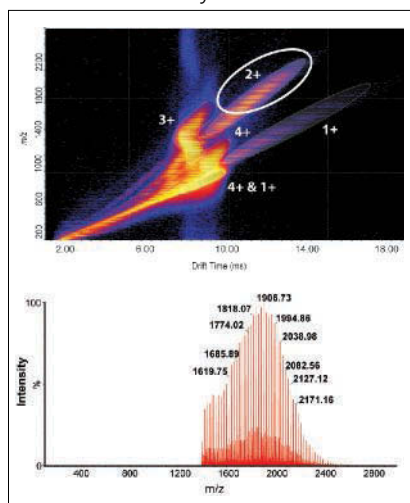
HeLa *Human cervical cancer cells*; an established cell line that is commonly used in biotechnology.

hemocytometer A device for counting blood cells.

hemoglobin A complex protein (a 4-mer) in red blood cells that binds and releases oxygen, carrying it from the lungs to all other tissues.

HEPA filtration High-efficiency particulate air filter used to remove contaminants

Visualization of a complex population of PEG structures by HDMS.



or to prevent particles from entering a clean room.

heterogeneity A term used to describe a biological component (i.e. protein) consisting of multiple structural variations.

HGH *Human growth hormone*; an early biopharmaceutical. Formerly derived from cadaveric pituitary glands, this protein is now produced by recombinant expression.

HIC *Hydrophobic interaction chromatography*; a type of liquid chromatography that makes use of the relative solubility of proteins and matrix materials. Hydrophobic interactions are strongest at high ionic strengths, so salt is usually included to increase those levels.

high-throughput screening Robotic methods used to sort through thousands of chemical compounds by running assays on many at a time.

Higher Order Structure (HOS) Structure relating to secondary, tertiary, or quaternary structure of a biomolecule, in contrast to its primary structure, the amino acid sequence.

His *Histidine*; one of more than 20 naturally occurring amino acids.

histochemistry A science that combines the techniques of biochemistry and histology to deal with the chemical changes and chemical constitution of tissues.

hit In drug discovery, a positive result in a high-throughput assay.

hormone A protein released by endocrine glands or sex organs to travel in the blood and act on tissues at another location in the body.

host A cell or organism used for growth of a virus, plasmid, or for the production of

cloned substances.

host cell protein(s) (HCP) Proteins from the host cell system used to manufacture a biopharmaceutical drug. Host cells contain hundreds to thousands of host cell proteins and other biomolecules that could contaminate the final product.

HPLC *High-performance liquid chromatography* or *high-pressure liquid chromatography*; a form of liquid chromatography in which a sample is forced at high pressure through a tube (column) that is packed tightly with chromatographic media.

human genome The complete set of human genetic instructions.

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.

hybridoma An immortalized cell line (usually derived by fusing B-lymphocyte cells with myeloma tumor cells) that secretes desirable antibodies.

Hydrogen Deuterium Exchange (HDX) Hydrogen deuterium exchange (HDX) with mass spectrometry (MS), also referred to as HX MS, is an important structural characterization tool for discovery and development stages. Uses in biotherapeutics include epitope mapping, binding, and protein–drug interaction studies, aggregation studies, effect of mutation on conformation, and localization of conformational changes. HDX provides information on the relative deuterium uptake of different conformations of a protein, or locations within a protein.

hydrolysis Literally “cleaved by water,”

a reaction in which the chemical bond attaching an atom or group of atoms to the rest of a molecule is severed, followed by attachment of hydrogen at the same point. Most often in biopharmaceuticals, the breakage of peptide bonds by addition of a water molecule.

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.

hydrophobicity The lack of an affinity for water.

hygroscopic Ready to take up and retain moisture.

I-J

ICH *The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use*; a project bringing together the regulatory authorities of Europe, Japan, and the United States with experts from the pharmaceutical industry to discuss scientific and technical aspects of product registration. Its purpose is to recommend ways to harmonize the technical guidelines and requirements for product registration and reduce or obviate the need to duplicate testing during development of new medicines.

Identity^E System A database search strategy for LC/MS^E data. LC/MS^E is a paral-



Insulin, a hormone, was the first biopharmaceutical approved by the FDA.

lel unbiased approach to data acquisition that increases both the number of peptides and also the reproducibility of the peptides sampled during an LC/MS experiment. The database search algorithm is for the qualitative identification of data originating from LC/MS^E data, whereby multiple precursor ions are fragmented simultaneously. Properties that are used by the algorithm include retention time, precursor and product ion intensities, charge state, as crucially the accurate masses of both the precursor and product ions form the LC/MS^E data.

IEC *Ion-exchange chromatography*; sometimes abbreviated IEX, a liquid chromatographic technique based on the electrical phenomenon of ion exchange. The amphoteric nature of proteins can be exploited to bind them in cation-exchange (binding positively charged proteins) or anion-exchange (binding negatively charged proteins).

IEF *Isoelectric focusing*; analytical separations in an electrical field through a pH gradient (therefore based on the net charge of the molecules); usually done in bioanalysis at a neutral pH so that proteins (for example) will move under the influence of the electric field until their net charge

is zero (their isoelectric point, pI). cIEF is a specialized form of electrophoresis that can be adapted to the capillary format.

IEX See also: IEC, ion-exchange chromatography.

Ile *Isoleucine*; one of more than 20 naturally occurring amino acids.

immortalize To alter cells (either chemically or genetically) so that they can reproduce indefinitely.

immunoassay An antibody-based test used most often for bioanalytical purposes.

immunodetection A process that identifies and quantifies specific biological substances, such as antigens.

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

immunoglobulin A protein produced by plasma cells that fights infection or takes part in various immune responses. Immunoglobulins bind with other molecules with a high degree of specificity; divided into five classes (IgM, IgG, IgA, IgD, and IgE) on the basis of structure and biological activity.

immunohistochemistry The staining of histology preparations using chromagen linked antibodies to specifically stain for specific proteins in a histology section/slide.

impurity A foreign agent or material either introduced as part of processing (such as buffers or salts added during chromatography) or intrinsic to the nature of bioprocessing (such as product variants and cellular debris).

in silico Studies done “in the computer.” Modeling a protein *in silico* refers to providing an integrated, computerized view of the

molecule.

in vitro Performed using laboratory apparatus rather than a living animal.

in vivo Involving living animals or humans as test subjects.

inclusion bodies Discrete structures (virions, viral components, cellular material, aggregated proteins) present either normally or abnormally within cells.

IND *Investigational New Drug application*; process by which a company files a request with FDA for permission to expose its experimental drug to patients or healthy human volunteers. This application must be filed for each individual clinical study performed, Phases 1 to 3.

indications A collection of symptoms or one disease type; the condition that a drug is intended to treat. The condition or symptoms a particular drug is used to treat are determined either by evidence of positive effect or knowledge of the cause of the disease.

infusion Introducing a solution into the bloodstream or another solution; also refers to the solution itself, such as a drug formulation, when infused.

intron Noncoding genetic information removed from pre-RNA in the formation of mRNA in eukaryotes.

inoculate To introduce cells into a culture medium; also to introduce material to sensitize patients (as in vaccination).

inoculum Material (usually cells) used to inoculate.

intact mass analysis A characterization technique using mass spectrometry that provides a mass measurement and an estimate of the overall heterogeneity of a protein.

intellectual property (IP) Any and all patent applications or patents, or trade secrets that make up the proprietary information of a company.

interferon A type of cytokine glycoprotein made by animal cells to inhibit virus reproduction to fight infection. Interferons also affect growth and development (differentiation) in certain normal and tumor cells.

interleukins Cytokines produced by lymphocytes or macrophages that modulate the immune response.

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

ion mobility separation (IMS) A technology that differentiates ions based on a combination of factors: their size, shape and charge, as well as their mass. IMS provides an orthogonal dimension of separation. Coupling of ion mobility measurements and separations with tandem mass spectrometry can be applied to the gas-phase structures of biomolecules. (See also HDMS)

iontophoretic delivery Introduction of drugs through intact skin using the transfer of ions by applying a direct electric current.

IQ *Installation Qualification*; documented verification that all aspects of a facility, utility, or equipment that can affect product quality adhere to approved specifications and are correctly installed.

IRB *Institutional review board*; a committee or other group (composed of medical, scientific, and nonscientific members) that is responsible for protecting the rights, safety, and well-being of human subjects participating in clinical trials.

isoelectric focusing An analytical technique that uses electrophoresis in a pH gradient (for example 4 to 10) to determine the isoelectric point (see also pI) of a polypeptide. May be performed in a gel, in a liquid, or in a capillary tube (cIEF).

isoform A specific and distinct structure or form of a biological molecule among a family of biological molecules with very similar structures and comparable, but not necessarily equal, action for the same product.

isolation chambers Laboratory chambers designed to protect workers from dangerous chemicals, organisms, or substances they are working with (or the reverse); includes hooded workstations, isolators, and clean rooms, for example.

isomerization Changes that create isomers (molecules with the same chemical make-up but a different structure), which alters the activity of most proteins.

isopycnic Describes molecules that have the same buoyant density in ultracentrifugation. Molecules of differing densities form different regions in equilibrium within a density gradient medium.

isotonic Having the same osmotic pressure as blood serum, thus easily mixed with the blood.

isotope An alternative form of an element having a different number of neutrons in its atomic nucleus.

K-L

kDa *kiloDalton*; a thousand Daltons.

knockout *Gene targeting*; for instance, a knockout mouse is one in which a single

gene is inactivated (“knocked out”), leaving other genes unaffected; provides the best way to delineate the function of a gene.

LAL assay *Limulus ameobocyte lysate assay*; detects pyrogenic endotoxins using a reagent that was discovered in the blood of *Limulus* horseshoe crabs.

laminar flow clean air device A clean bench, clean workstation, and wall or ceiling modules or other devices that incorporate a filter and motor blower for supplying clean air in one direction for a controlled work space; more correctly referred to as “unidirectional airflow,” which is air flow having generally parallel streams operating in a single direction and with uniform velocity over its cross section.

LC/MS systems *Liquid chromatography/mass spectrometry systems*; laboratory instruments that combine two popular analytical methods into one piece of equipment.

LC/IMS/MS systems *Liquid chromatography/ion mobility/mass spectrometry systems*; laboratory instruments that combine three popular analytical methods into one piece of equipment.

LC/MS/MS Liquid chromatography with tandem mass spectrometry detection; a highly selective method using an atmospheric-pressure ionization tandem mass spectrometer to measure the difference in the mass-to-charge ratio of ionized molecules and fragments.

leachable Chemical entity that has the potential to be extracted from a container or closure when exposed to certain conditions of solutions. Examples of common leachables seen in pharmaceuticals include plasticizers, metals, accelerating agents.

Leachables are potential extractables, and may be evaluated by USP standard tests.

lead 1. A molecule that modulates the activity of a receptor or other target protein. Successful lead compounds become candidates for drug development. 2. Pb, a toxic heavy metal.

legacy system Old hardware and software applications in which a company has already invested considerable time and money, and which is no longer state-of-the-art or compliant with regulatory requirements.

Leu *Leucine*; one of more than 20 naturally occurring amino acids.

ligands Molecules or ions that chemically bind to certain other molecules or ions. In a binding action, usually the smaller of the two molecules is considered the ligand.

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.

LIMS *Laboratory information management system*; computers and software that handle all the data produced by laboratory research and analytical methods.

liquid chromatography Analytical method used to separate mixtures of substances based on the differential distribution of the substances between a stationary phase (material such as silica gel or silicic acid, usually contained in a column, tube, or capillary) and a liquid mobile phase (a medium that carries the sample through

the stationary phase). This very effective technique can separate substances that are nearly identical.

liquid fractionation Any of several precipitation or phase-separation methods used to determine the molecular weight distribution of polymers, based on the tendency of polymers of high molecular weight to be less soluble than those of low weight.

lot A GMP-defined word used to refer to an entire batch of product.

lot release testing Samples from each drug lot (batch) manufactured for clinical trials or (later on) for sale are tested to prove that the batch meets specifications for content and purity before it is released for use.

luciferase In luminiscent organisms (fireflies, some bacteria, and certain marine organisms), luciferase is an enzyme that acts on species-specific light-emitting substances known as luciferins. Chemiluminescent assay systems using firefly luciferin–luciferase have detected small amounts of ATP, the energy-storage compound of a cell. Such systems may serve as alternatives to radioimmunoassays and fluorescence methods.

lymphocytes White blood cells that produce antibodies.

lyophilization Freeze-drying; a procedure by which a liquid solution is frozen to a glassy state (primary drying), then slightly heated to remove the unfrozen water by sublimation.

Lys *Lysine*; one of more than 20 naturally occurring amino acids.

lysed-cell slurry A mixture of the debris formed by disintegrating or breaking cells.

lysis Disruption or breaking of the

cellular membrane of cells by chemical, enzymatic, or mechanical means. A solution containing the contents of lysed cells is called a “lysate.”

lysosomes Cell organelles containing enzymes, responsible for degrading proteins and other materials ingested by the cell.

M

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

MAC *Mammalian artificial chromosome*; a vector used to clone DNA fragments larger than 100,000 base-pairs long. As suggested by the name, MACs are constructed from mammalian cell DNA.

macrokinetics Movement of whole cells and their media within a bioreactor.

macromolecules Very large molecules (proteins, carbohydrates, nucleic acids), often formed by two or more identical molecules in a chain configuration (polymers).

MALDI-TOF *Matrix-assisted laser desorption ionization–time of flight*; mass spectrometry technique for determining molecular weight. Electrons become excited after laser irradiation, transferring energy into the mixture and causing molecules and ions to be ejected from its surface. Commonly used in proteomic and peptide analyses.

mannitol A sugar alcohol (found naturally in many plants, algae, and fungi) that is obtained by reducing mannose and used as a pharmaceutical excipient and in diagnostic tests of kidney function.

mannose A sugar (an aldohexose) often used as an excipient in drug formulations.

mass spectrometry Mass spectrometry (MS) is an analytical technique that measures the mass-to-charge ratio of charged particles. It is used for determining masses of particles, for determining the elemental composition of a sample or molecule, and for elucidating the chemical structures of molecules, such as peptides and other chemical compounds. The MS principle consists of ionizing chemical compounds to generate charged molecules or molecule fragments and measuring their mass-to-charge ratios.

master batch record The template that describes the step by step procedures to be followed during manufacturing, with spaces to record actual data. The master batch record is uniquely identified, under change control, pre-approved by quality assurance, and used to generate each individual batch record that is issued when a given batch is to be manufactured.

master cell banks A master cell bank is prepared by culturing a homogeneous population of cells, such as an established, cloned cell line, under defined conditions and then distributed into containers in a single operation, processed together to ensure uniformity, and stored to ensure stability. Each vial is presumed to have comparable properties, and thus the bank may be characterized by testing a representative number of individual vials. Cell cultures derived from the master cell bank are used to prepare working cell banks for manufacturing of a biopharmaceutical. Both master and working cell banks are extensively tested and characterized before

use. (See working cell bank)

media Plural form of medium, a (usually sterile) preparation made for the growth, storage, maintenance, or transport of microorganisms or other cells.

Met *Methionine*; one of more than 20 naturally occurring amino acids.

metered dose inhaler (MDI) A device used to deliver a fixed volume or dose of an aerosol form of an active drug substance to the lungs and/or bronchi.

metabolism Drug metabolism is the biochemical modification of pharmaceutical substances by living organisms, usually through specialized enzymatic systems. This is a form of xenobiotic metabolism. Drug metabolism often converts lipophilic chemical compounds into more readily excreted polar products. Its rate is an important determinant of the duration and intensity of the pharmacological action of drugs.

metabolites Chemical products of metabolism, the chemical process of life.

micelle A spherical arrangement (bubble) formed by a group of lipid molecules in an aqueous environment; hydrophobic ends of the molecules are turned inward and hydrophilic ends are turned outward. A molecular aggregate that constitutes a colloidal particle (a substance consisting of particles dispersed throughout another substance with particles too small for resolution with an ordinary light microscope, but that can pass through a semipermeable membrane).

microassays Assays usually run on very small samples, often using “microplates,” and often automated. Microplates can have room for 96, 384, or even 1,536 tiny samples. Microassays measure small quanti-

ties of components even when the sample size is large.

microbial fermentation Processes involving the use of microorganisms, such as *E. coli*, to produce a protein or other substance.

microbial testing Analytical methods required by regulations to ensure sterility and to measure bioburden or identify microorganisms in controlled, classified environments.

microbiology The study of microscopic life such as bacteria, viruses, yeast, and protozoa.

microcarrier A microscopic particle (often a 200 μm polymer bead) that supports cell attachment and growth in suspension culture; alternative to microencapsulation. Cells anchor into tiny pores on the beads for protection.

microencapsulation In cell culture, trapping cells inside a thin protective membrane to provide anchorage and protect them from harsh conditions. Microspheres are often biodegradable.

microfiltration A method of sterile filtration, clarification, or cell harvesting that removes particles in the 0.1 to 10.0 μm range.

microheterogeneity In biopharmaceuticals, 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 Met must be added to one end of the protein sequence to act as a signal that initiates protein synthesis. In most cases, that Met is removed once the protein is made. Sometimes the Met is removed

from 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.

microinjection Manually using tiny needles to inject microscopic material (such as DNA) directly into cells or cell nuclei; video screens provide a magnified view.

micron See micrometer. The preferred term is micrometer.

micrometer One millionth of a meter's length. Abbreviated as μm .

microorganism A microbe; a free-living organism too small to be seen by the naked eye.

microspheres Tiny polymer spheres (usually biodegradable) measured in micrometers.

miRNA A single-stranded RNA molecule of about 21 to 23 nucleotides in length, which regulates gene expression.

mitochondria Animal-cell organelles that reproduce using their own DNA. They metabolize nutrients to provide the cell with energy and are believed to have once been symbiotic bacteria. Chloroplasts are their plant-cell equivalents.

MOBCAL Software that calculates mobilities. MOBCAL is an open-source software and is command-line driven (www.indiana.edu/nano/software.html).

moiety One of the portions into which something is divided; a component, part, or fraction. In chemistry, a specific section of a molecule, usually complex, that has a characteristic chemical effect or property.

mole The amount of a substance that contains the same number of elements (such

as atoms, molecules, or ions) as there are atoms of carbon in 12 grams of carbon-12; one mole contains Avogadro's number of molecules (6.02×10^{23}).

monomer A simple molecule that may combine with others to form polymers.

monosaccharide (see carbohydrate)

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.

MSDS *Material safety data sheets*; documentation (including data describing physical characteristics, toxicity, health effects, first aid, reactivity, storage, disposal, protective equipment, and spill/leak procedures) that provides workers and emergency personnel with the proper procedures for handling or working with a particular substance.

MSE^E The simultaneous acquisition of exact mass data using alternating collision cell energies. This technique is unique to Waters mass spectrometers, which can perform this simultaneous data capture at UPLC speed (see also UPLC). The MSE^E approach, when used to acquire precursor and product ion information, has the additional benefits of obtaining both types of data in one analytical run. Both the precursor and product ion data are acquired in accurate mass mode so that elemental composition information can be generated from both sets of data. Another advantage of MSE^E is that neutral loss information from a comparison of the two alternating collision energy scans can be obtained, eliminating the need for any further experimentation. The mode of operation also removes the need for time-consuming re-

analysis to obtain both MS and MS/MS data. Data acquired in MSE^E mode can be mined at a later date for different information.

multicellular Referring to organisms composed of more than one cell—often billions of them—arranged in various organs, tissues, and systems.

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

multimer formation Association of peptide or protein molecules to produce dimers (two linked identical molecules), trimers (three linked identical molecules), and so on depending on how many identical molecules link up together

mutagen An agent (chemicals, radiation) that reacts with DNA to produce mutations.

mutagenicity The degree to which a substance can cause a change in an organism's DNA.

mutation A permanent change in DNA sequence or chromosomal structure.

MW *molecular weight*; refers to the mass of a molecule, usually stated in Daltons.

mycoplasma Parasitic microorganisms that infect mammalian cells, possessing some characteristics of both bacteria and viruses. Prokaryotic microorganisms, family Mycoplasmataceae, with no cell walls (therefore resistant to many antibiotics) and needing sterols for maintenance and growth. Potential contaminants of mammalian cell cultures, they may grow attached or close to cell surfaces in the cytoplasm, subtly altering properties of the cells, but escaping detection unless specifically monitored. In cell culture of biopharmaceuticals, each lot must be tested at the end of cell culture for

mycoplasma contamination; a confirmed positive results in batch rejection.

myeloma Lymphocytic cancer; a malignancy found in bone marrow.

N

native The natural state; in a biopharmaceutical context, it usually refers to a molecule's normal three-dimensional structure under optimal conditions.

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.

nebulizer A device, pressurized by an oxygen or nitrogen tank, for the purpose of converting a liquid (such as a medicinal formulation) into a fine mist (to be inhaled, for example).

nick translation A technique used to introduce radioactively and nonradioactively labeled nucleotides into DNA; the new nucleotide is added at the position where the original nucleotide was excised; nick translation can be used for a number of hybridization techniques, such as gel blots and colony plaque lifts.

NIH *National Institutes of Health*; the US government agency that conducts and supports medical research and dissemination of information. One of eight agencies in Public Health Services, which is in turn part of the US Department of Health and Human Services.

NIR spectroscopy *Near-infrared spectroscopy*; a bioanalytical technique that

uses radiation in the near-infrared range to provide rapid, nondestructive analysis of materials.

NIST *National Institutes of Standards and Technology*; a federal agency that develops and certifies standard reference materials for use in various US industry applications

NMR spectroscopy *Nuclear magnetic resonance spectroscopy*; an analytical method that generates a spectrum (based on the electromagnetic environment surrounding the nucleus of each atom in a molecule) that serves as the chemical signature of each molecule and aids in structure determination.

nonconformity A deficiency in a characteristic, product specification, process parameter, record, or procedure that renders the quality of a product unacceptable, indeterminate, or not according to specified requirements. [From FDAQSG]

norleucine An amino acid, not produced by mammalian cells, but may be produced by many bacteria, especially under conditions of nutrient-poor media. NorLeu may be substituted for Leu when a mammalian protein is expressed in bacterial cells, creating new product variants that may be of safety concern.

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.

nucleosides Glycosylamines consisting of a nucleobase bound to a ribose or deoxyribose sugar. The most prevalent examples of nucleosides are adenosine, cytidine, guanosine, thymidine, and uridine.

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). These molecules comprise the basic structural units of RNA and DNA.

nucleus The largest organelle, a membrane-bounded compartment found in eukaryotes that contains most of the cell's genetic material and a nucleolus that builds ribosomes.

O

oligomer A short polymer consisting of a few monomers, typically refers to small nucleotide polymer.

oligonucleotide A short nucleotide polymer, typically with 30 or fewer bases.

oligosaccharide (see carbohydrate)

Omega (Ω) The value of Omega is square angstroms (\AA^2). Omega can be calculated theoretically for any ionic structure based a three-dimensional structure. Historically, a physical model of the molecule was constructed and mounted between a light source and a screen. The area of the shadow was measured for many orientations and then an average calculated. The measurement of Omega provides a mechanism for comparison of different (ionic) species for this attribute.

oncogene A gene that, when expressed, can lead cells to become cancerous, by removing the normal constraints on their growth.

OOS *Out-of-specifications result*; a result that is outside the range of an approved specification. An OOS result must be investigated to determine whether it is due

to laboratory error, operator error, or process error; and a judgment made whether the result itself is valid (accurate estimate of the true value of the analyte) or invalid. Usually, confirming an OOS result as valid results in affected lot(s) of product being rejected.

OOT *Out of tolerance*; 1. refers to equipment or instrument which, when its calibration is checked, is outside of a defined range and requires adjustment or repair. 2. *Out of trend*; a test result that is unexpected or outside of its historical or statistical trends but within specifications; and must be investigated as a type of exception. The investigation is very similar to an OOS investigation, with the difference that product disposition may not be affected by a confirmed out of trend result.

operon A group of functionally related, adjacent genes found in prokaryotes that operate as a unit to synthesize functionally related proteins (enzymes). An operon group includes an operator region, a regulator gene, and structural genes equivalent to the number of enzymes in the system.

optimization Determining and implementing process operation at the best possible and most affordable efficiency.

OQ *Operational Qualification*; documented verification that all aspects of a facility, utility or equipment that can affect product quality operate to Intended throughout all anticipated ranges.

organelle A structurally discrete component that performs a certain function inside a eukaryotic cell.

organic In chemistry, any molecule containing carbon atoms is considered an organic molecule (from the Greek for "work").



Peptide mapping provides detailed structural information for a protein; it is a challenging application because of the number of peaks that must be baseline-resolved. The Waters ACQUITY UPLC H-Class Bio System, with Peptide Separation Technology Columns, provides maximum LC resolution and sensitivity for more confidence in protein characterization studies.

Organic chemistry is the chemistry of life because carbon interacts in myriad ways with a large number of other elements to form complex molecules (RNA, DNA, amino acids, proteins, and so on) that perform the intricate actions that make life “work.”

organism A single, autonomous living thing. Bacteria and yeasts are organisms; mammalian and insect cells used in culture are not.

orphan drug A US product that treats a rare disease affecting fewer than 200,000 people.

orthogonal At right angles or differing completely. Sometimes used to mean occurring stepwise rather than simultaneously.

osmolarity The concentration of osmotically active particles in a solution (expressed in osmoles of solute per liter of solution). Osmosis is flow through a semipermeable

membrane under the influence of an osmotic gradient. Osmotic pressure is the pressure that must be applied to a solution to prevent osmosis. Osmotic shock is a rapid change in osmotic pressure on a cell or virus, usually causing it to discharge its contents.

outsourcing Having research, laboratory testing, clinical trials, or manufacturing done by another firm, usually called the contract organization. (See sponsor; quality agreement)

overflow The liquid portion of a broth after centrifugation when solid particulates have settled out; describes the part of the centrifuge apparatus that holds the liquid separate from the solids (the underflow).

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

P

PA *projection approximation*; an ion is modeled by a collection of overlapping hard spheres with radii equal to hard sphere collision distances. The orientationally averaged geometric cross section is determined by averaging the geometric cross section over all possible collision geometries.

PAI *Preapproval inspection*; an FDA facility inspection performed in response to a biopharmaceutical company’s filing an NDA. (See prelicense inspection)

parenteral delivery Drug delivery by

injection; subcutaneous, intra-muscular, and intravenous delivery are most common. Drug must be sterile.

particle filtration Particle filtration is used to filter macro particles, which are visible to the naked eye and range in size from 50 μm to 1000 μm . Examples of particles in this size range include beach sand, granular activated carbon, human hair, mist, pollen, milled flour, and precipitates formed during bioprocessing.

passage number When cells are cultured, the passage number is a theoretical number of cell generations, or how many times the cells have been “passed” *in vitro*.

PAS *Pre-approval supplement*; a regulatory submission to FDA used for biologics and biopharmaceuticals when major changes to the process, facility, or quality control system are desired. The sponsor must wait for full FDA review and approval before any product manufactured may be placed in distribution. Often, a PAS or a CBE-30 may be part of a comparability protocol, and the type of submission required for a given package of changes is negotiated with FDA by RA personnel.

PAT See process analytical technology.

PCR *Polymerase chain reaction*; a process that exponentially amplifies (reproduces) a short piece of DNA having a specific nucleotide sequence, making possible many research and clinical applications involving that DNA (used extensively in forensics). PCR may be qualitative or quantitative (qPCR).

peak An individual component of a mixture that is washed out of the chromatography column during elution (the

elution fraction). The sharp rise in the line graph of a chromatogram that represents this phenomenon.

PEG *Polyethylene glycol*; a polymer that usually consists of a size distribution of various molecular weight compounds. Physical and chemical properties vary with the molecular weight (liquid to solid, viscosity, etc.). PEGs are used as surfactants in industry (for foods, cosmetics, and pharmaceuticals); and in biomedicine as dispersing agents, solvents, ointment and suppository bases, vehicles, and excipients.

PEGylation Covalent attachment of polyethylene glycol molecule(s) to a protein molecule via 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 bioanalysis The use of analytical techniques to quantitatively measure peptide drugs and their metabolites in biological systems. Formerly performed using ligand-binding assays such as radioimmunoassay and ELISAs, LC/MS/MS is now being applied to peptide bioanalysis for its higher accuracy levels. A successful, highly sensitive method for the analysis of peptides relies upon a combination of high-performance chromatography, mass spectrometry, and sample preparation.

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 Short polymers formed from the linking, in a defined order, of amino acids. The link between one amino acid residue and the next is known as an amide bond or a peptide bond.

perfusion Sometimes perfusion propagation; a cell culture or fermentation process commonly used in antibody production, in which high concentrations of mammalian cells inside a chamber have fresh growth media continually circulated around them for continuous addition of nutrients and removal of waste products.

permeate Also called filtrate, the part of a mixture that passes through a filter.

pH Power of hydrogen or the log of the concentration of H⁺ ion in a solution. Measurement of the relative alkalinity or acidity of a solution. Pure water is pH neutral (7), acidic solutions have pH values between 0 and 7, and alkaline or basic solutions have pH values between 7 and 14. Often a critical control parameter in biopharmaceutical processes.

phage A virus-like parasite that infects bacteria; also bacteriophage.

pharmaceutical development Collected information from development studies conducted to establish that the dosage form, formulation, manufacturing process, and quality attributes are appropriate for the product. The development process should

identify and describe the critical quality attributes and critical process parameters that influence product quality and performance.

pharmacodynamics Study of the reactions between drugs and living structures, including the processes of bodily responses to pharmacological, biochemical, physiological, and therapeutic effects. A PD study seeks to determine where a drug penetrates in the body and by means of what mechanisms.

pharmacokinetics Sometimes abbreviated as PK, (from Ancient Greek *pharmakon* “drug” and *kinetikos* “to do with motion”; see chemical kinetics) is a branch of pharmacology dedicated to the determination of the fate of substances administered externally to a living organism. The substances of interest include pharmaceutical agents, hormones, nutrients, and toxins. (See also ADME.)

Phe *Phenylalanine*; one of more than 20 naturally occurring amino acids.

phenotype The observable characteristic that results from the action of an organism’s genes. Phenotype varies depending on which

In pharmaceutical development, analysts generate information-rich and reliable analytical methods to support IND and NDA submissions for innovative medicines.



alleles of each gene are present.

phosphoramidite or nucleoside phosphoramidites The individual base building blocks that are used to synthesize short nucleic acid chains also known as oligonucleotides.

phosphorylation Addition of a phosphate (PO₄) group to a molecule, usually enzymatically done by transferring a phosphate group from ATP (adenosine triphosphate).

physical state The form that matter takes, whether solid, liquid, gas, or plasma.

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.

Pichia pastoris An alternative yeast species proposed as a recombinant expression system. It performs post-translational modifications that are more similar to human protein modifications than those performed by other yeasts used in fermentation.

pilot plant A medium-scale bioprocessing facility used as an intermediate in scaling up processes from the laboratory to commercial production.

placebo A fake treatment (usually the same formulation used for the real product, but without the active ingredient) administered to the control group in a controlled clinical trial so that the specific and nonspecific effects of the experimental treatment can be distinguished. The experimental treatment must produce better results than the placebo to be considered effective.

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.

polar solvent A solvent for molecules that have permanent electric dipoles.

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

polyacrylamide A high molecular-weight polymer of acrylamide (a neurotoxin) used as a support and separations matrix in electrophoresis and gel chromatography.

polymer A large molecule formed by the combination of at least five (and sometimes as many as 1,000) identical smaller molecules (monomers).

polymerase An enzyme that catalyzes the production of nucleic acid molecules.

polymerize To undergo or subject to polymerization, a chemical reaction in which two or more molecules combine to form larger molecules that contain repeating structural units.

polymorphism A single mutation in a gene at one nucleotide locus that potentially changes gene expression with a modified protein that may possess different properties, for example, the activity of an enzyme with a drug.

polysaccharide A kind of complex carbohydrate (macromolecule composed of long chains of simple sugars). Several polysaccharides from microorganisms have

important commercial uses.

polyorbate 80 A hydrophilic surfactant commonly used as a pharmaceutical excipient, among other things.

polysorbates Complex mixtures of polyoxyethylene ethers used as emulsifiers or dispersing agents in pharmaceuticals.

polyvinyl A polymer prepared from polyvinyl acetates by replacement of the acetate groups with hydroxyl groups. It is used as a pharmaceutical aid (a substance with little or no therapeutic value that is necessary in the manufacture, compounding, or storage of pharmaceutical preparations or drug dosage forms). Polyvinyls are used as solvents, diluting agents, suspending agents, and emulsifying agents.

polyvinyl alcohol A synthetic polymer used as a fixative and an adhesive and as an emulsifying agent, thickener, and stabilizer. Specimens can remain in PVA without damage for long periods of time.

postapproval changes Changes (scale-up, for example) made to a biopharmaceutical manufacturing process after the drug has been approved for marketing.

postmarketing surveillance Phase 4 clinical trials, which provide additional details about a product's safety (while the product is on the market) and efficacy and may be used to evaluate formulations, dosages, durations of treatment, medicine interactions, additional indications, and other factors.

post-translational modification (PTM) 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



Laboratories rely on the high purity and recovery achieved with preparative chromatography columns.

protein processing is done by the Golgi bodies after proteins have been constructed by ribosomes.

potency The measure of the biological activity using a suitably quantitative biological assay (also call potency assay or bioassay), based on the attribute of the product that is linked to the relevant biological properties. [From ICH Q6B]

PQ *Performance qualification*; Documented verification that all aspects of a facility, utility or equipment perform as intended in meeting predetermined acceptance criteria.

pre-license inspection An FDA facility inspection performed in response to a biopharmaceutical company's filing of a BLA to confirm claims made in the license application and assess the readiness and cGMP compliance of the manufacturing plant.

precipitation Process causing a solid to settle out of solution (as in centrifugation) by the action of gravity or by a chemical reaction; a reaction between a soluble antibody and a soluble antigen, resulting in the formation of a substance (known as a precipitate) that separates, in solid particles, from a liquid.

preformulation An exploratory activity that begins early in biopharmaceutical

development, involving studies designed to determine the compatibility of initial excipients with the active substance for a biopharmaceutical; physicochemical and bioanalytical investigation in support of promising experimental formulations.

preparative chromatography Chromatography methods used in manufacturing rather than analytical applications, larger in scale and intended to purify a product; also called process chromatography. Chromatographic methods were first used in analytical laboratories, and only later in the 20th century were they adapted to industrial separations use. (Contrast with small-scale analytical chromatography.)

preservative A chemical additive that prevents spoilage by killing or inactivating microorganisms; also stabilizes molecules such as when using antioxidants or sulfhydryls to stabilize proteins. (Contrast with bacteriostatic agent, which prevents microbes from multiplying but does not kill them).

primary recovery The early steps in separation and purification of a biopharmaceutical, in which a complex biological solution containing the protein of interest is concentrated and clarified, usually by means of filtration, centrifugation, or extraction (precipitation); and the protein of interest is isolated from residual debris, cells, and other macromolecular materials.

primary structure The amino acid sequence of a biomolecule.

prion Believed to be the smallest, simplest infectious particle consisting of a hydrophobic protein (no nucleic acid, DNA, or RNA), suggested as a possible model for the causal agent of scrapie and related diseases,

called TSEs. (Term originally derived from proteinaceous infectious particle.)

Pro *Proline*; an imino acid often grouped with the 20 naturally occurring amino acids.

process analytical technology (PAT)

A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality. [From ICH Q8]

process control 1. The means by which a process is monitored and operated, and is designed to maintain critical parameters within set ranges determined to be safe. 2. A consistent process that follows predictable statistical trends and is monitored using control charts is said to be in a state of “statistical control.”

process development The step in the life cycle of a product that starts with information from research, and delivers a scalable process to manufacturing plants that can be validated, operated under cGMP controls, and be commercially viable. During process development, preclinical and clinical trial supplies of the product are manufactured.

process knowledge A compilation of all facts about a manufacturing process from development through full-scale manufacture.

process-related impurities Impurities that are derived from the manufacturing process. They may be derived from cell substrates (e.g., host cell proteins, host cell DNA), cell culture (e.g., inducers, antibiotics, or media components), or downstream processing (e.g., processing reagents of column

leachables). [From ICH Q6B]

process robustness Ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality. [From ICH Q8]

process understanding Comprehension of process knowledge such that all critical sources of variability are identified and explained; variability is managed by the process; and product quality attributes can be accurately and reliably predicted over the design space established for the materials and process. Through process understanding, process performance and product attributes can be explained logically and scientifically as a function of process parameters, inputs, and input material attributes.

product lifecycle All phases in the life of the product, from the initial development through marketing until the product's discontinuation. [From ICH Q9]

prodrug A modified version or precursor of a parent compound designed to enhance delivery properties and be converted to the parent compound in the body.

product-related impurities Molecular variants of the desired product (e.g., precursors, aggregates, certain degradation product arising during manufacture and/or storage) that do not have properties comparable to those of the desired product with respect to activity, efficacy, and safety. [From ICH Q6B]

product-related substances Molecular variants of the desired product formed during manufacture and/or storage that are active and have no deleterious effect on the safety and efficacy of the drug product. These variants possess properties compa-

ble to the desired product and are not considered impurities. [From ICH Q6B]

product specification A list of tests and acceptance criteria (limits) that are used to define the quality of a drug substance or drug product. The specification is often listed on the Certificate of Analysis along with results for a specific batch or lot.

product variant A molecule that is related to the product but differs from it chemically, such as a degradation product, intermediate, or different configuration of the protein of interest due to deamidation or other chemical reactions. A product variant is form (charge isoform, n- or c-terminal form, eglycoform, etc.) that is considered part of the product definition.

prokaryotes Simple organisms, such as bacteria, with no cell nuclei and only a few cell organelles.

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.

proteinase K A serine protease (used in molecular cloning and DNA sequencing, nucleic acid research, and protein and peptide structural analysis) with broad specificity toward aliphatic, aromatic, and other hydrophobic amino acids, cleaving their peptide bonds.

protein conformation The characteristic three-dimensional shape of a protein, including the secondary, tertiary, and quaternary structure of the peptide chain.

protein folding A rapid biochemical reaction involved in the formation of

proteins. It begins even before a protein has been completely synthesized and proceeds through discrete intermediates (primary, secondary, and tertiary structures) before the final structure (quaternary structure) is developed.

protein truncation Shortening a polymeric chain of amino acids; the protein truncation test developed by Dutch researchers screens proteins to identify abnormally short molecules that suggest the location of genetic mutations.

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 protoplasts (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).

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

proteolytic Capable of lysing (denaturing, or breaking down) proteins.

proteome The complete listing and description of all the proteins and their functions for an organism.

proteomics Study of protein function and structure.

protocols Documentation (submitted to FDA or other agency in support of regulatory filings) that directs the work performed in an FDA-regulated company. Protocols tell who directs which activities, who approves what, and who is allowed to sign off on materials and products, even where to find specific files and documents—all tying together numerous SOPs.

PTC *Points to Consider*; PTC documents are not regulations with the force of law, but are instead guidelines on issues that FDA believes should be considered by regulated industry. These documents are not definitive or all-inclusive. In fact, they are presented as drafts subject to further modification, and readers are invited to submit comments. They acknowledge that processes and associated knowledge change with time. They suggest and recommend procedures that manufacturers should consider during development of new drugs and biologics.

purification A central part of downstream processing that takes a crude fermentation supernatant or cell homogenate (a chaotic slurry of tissues and cells) and isolates the product from it in a fairly pure form.

pyrogen Any fever-inducing (pyrogenic) substance; more specifically, a lipopolysaccharide (the major constituents of the cell walls of Gram-negative bacteria). The major endogenous pyrogen in mammals is probably interleukin-1, production of which is stimulated by lipopolysaccharide.

pyrogenic endotoxins Components of bacteria (such as lipopolysaccharides)

that induce a feverish immune response in higher organisms.

Q-R

QA *Quality assurance*; 1. 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. 2. The sole work unit that is empowered to disposition drug product and drug substance (release or reject) for use in humans; and that provides and sustains quality systems such as document control, corrective and preventive actions, audits and oversight.

QC *Quality control*; 1. the system of testing that confirms and measures the quality of raw materials, process intermediates, final product, and environmental samples, during ongoing production as well as during start-up and validation. 2. The work unit that usually performs testing regulated under cGMP and evaluates results against specifications, action limits, or targets, and makes technical recommendations to QA. May be in the same department as QA in some organizations.

QTof A hybrid mass spectrometer design that couples time-of-flight (TOF) instrument with a quadrupole. This pairing results in a combination of performance characteristics: accurate mass measurement, the ability to carry out fragmentation experiments, and high quality quantitation.

quadrupole mass analyzer One type of mass analyzers used in mass spec-

trometry. It consists of four circular rods, set perfectly parallel to each other. Ions are separated in a quadrupole based on the stability of their trajectories in the oscillating electric fields that are applied to the rods, thus filtering the sample ions based on their mass-to-charge ratio.

qualification 1. Documenting that a piece of equipment does what it was designed to do, was installed correctly, and continues to operate within specified parameters over time. 2. A term used during process or analytical development to describe the experiments that are done prior to validation of the assay or process, that define the critical parameters and design space. 3. Analytical instruments are qualified to ensure fitness for intended use (USP <1058>). See also DQ, IQ, OQ, PQ. This term sometimes is used interchangeably with “validation.”

quality The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity (from ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances). [From ICH Q8]

Quality by Design (QbD) A term defined by the ICH quality guidelines, meaning the use of science, engineering, and statistical tools, as appropriate, to design quality into a process or product, or device; and to ‘mistake-proof’ or design out common errors.

quality risk management A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the

product lifecycle. [From ICH Q9]

quality system A series of processes that are linked together and controlled centrally to increase assurance of product or manufacturing process quality. Term used by FDA, ICH, and ISO to define those systems that are created and maintained by QA to support GMP operations. Examples include documentation, facility, equipment, packaging, and labeling.

quaternary protein structure The defined organization of two or more macromolecules with tertiary structure such as a protein that are held together by hydrogen bonds and van der Waals and coulombic forces.

radiolabeled Covalently labeled with a radioactive isotope or substance.

R&D *Research and development*; discovering and developing new products; the department within a company that does so.

raw material Term with differing definitions in different documents; commonly means all materials that are used to manufacture a drug substance or drug product, and regulated by 21 *CFR* 84. (See also components, starting materials).

reanneal The process of renaturing complementary single-stranded DNA molecules to yield duplex molecules.

recall Product recall; the act of locating all units of a given lot of product that have been placed in the distribution chain for human use and “recalling” them, for cause. Recalls are classified based on a risk assessment. (See also withdrawal)

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 also transgenics)

recovery Purifying a molecule of interest from the mix of biological components produced by a biotech manufacturing fermentation or cell culture process.

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

reducing agent A molecule that donates an electron in an oxidation-reduction reaction, which is a chemical change in which one species is oxidized (loses electrons) and another species is reduced (gains electrons). Reducing agents such as active metals (sodium, magnesium, aluminum, and zinc) can be used to take the place of proteins and keep them from being oxidized.

regeneration (of a column) The act of stripping and cleaning a chromatographic resin of any bound product or contaminants, then stabilizing the surrounding environment in preparation for reuse, usually done by a sequence of various solvents or buffers.

regulatory affairs Drug companies must show that their products consistently meet standards set by government agencies and that manufacturing stays within approved boundaries defined in the license application. Regulatory affairs departments document those activities, submit proposals, and follow those proposals through

completion or approval. RA provides regulatory strategy, and sets up meetings with regulatory bodies, and determines when formal notification or submissions to FDA and other regulatory bodies are required. RA is also involved during product recalls or withdrawals.

reproductive toxicology Studies of a drug substance in certain animal models to look for any impact on the test animals' reproductive function.

requirements The explicit or implicit needs or expectations of the patients or their surrogates (e.g., healthcare professionals, regulators and legislators); includes not only to statutory, legislative, or regulatory requirements, but also such needs and expectations. [From ICH Q9]

residue An amino acid when referred to as part of a polypeptide chain.

resin Any of several solid or semi-solid inflammable substances, of natural or synthetic organic origin; usually translucent polymers that do not conduct, that break like glass, and that are soluble in ether, alcohol, and essential oils but not in water. The word is used generically to describe chromatographic media, particularly polymer beads.

resolution A measure of the distinguishability of individual elements (the component parts of a mixture, for example). In chromatography, the quality of separation measured in terms of the purity of the resulting component fractions (higher resolution means greater purity).

restriction enzyme A bacterial enzyme that cuts DNA molecules at discrete base-pair locations.

retentate The part of a mixture that is

held back by a filter because of its size, shape, and/or charge.

retention time The period of time between initial application of an elution buffer and the exit from the column of a particular sample component.

reversed-phase chromatography An elution procedure used in liquid chromatography in which the mobile phase is significantly more polar than the stationary phase, e.g., a microporous silica-based material with alkyl chains chemically bonded to its accessible surface.

RIA *Radioimmunoassay*; a bioanalytical method that uses specific antibodies and radiolabeled detector molecules to quantitate a defined analyte in mixtures. For safety considerations, many immunoassays are now performed using dyes or other markers in lieu of the radioactive label.

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.

RNAi *RNA interference*; a system that regulates what genes are active and how active they are. Two types of RNA molecules, microRNA (miRNA) and small interfering RNA (siRNA), are central to RNA interference.

risk The combination of the probability of occurrence of harm and the severity of that harm. [From ICH Q9; see also ISO/IEC Guide 51]

risk acceptance The decision to accept risk. [From ICH Q9; see also ISO Guide 73]

risk analysis The estimation of the risk associated with the identified hazards. [From ICH Q9]

risk assessment A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. [From ICH Q9]

risk communication The sharing of information about risk and risk management between the decision maker and other stakeholders. [From ICH Q9].

risk control Actions implementing risk management decisions. [From ICH Q9; see also ISO Guide 73]

risk evaluation The comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk. [From ICH Q9]

risk identification The systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description. [From ICH Q9]

risk management The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating, and reviewing risk. [From ICH Q9]

risk reduction Actions taken to lessen the probability of occurrence of harm and the

severity of that harm. [From ICH Q9]

risk review Review or monitoring of output/results of the risk management process considering (if appropriate) new knowledge and experience about the risk. [From ICH Q9]

robust Strongly formed or constructed, sturdy; a product or process that doesn't break easily or remains stable and (for a process) reproducible despite physical and chemical stress or varying conditions.

roller bottle A container with large growth surfaces in which adherent cells can be grown in a confluent monolayer. The bottles are rotated or agitated to keep cells in contact with growth media, but they require extensive handling, labor, and media. In large-scale vaccine production, roller bottles have been replaced by microcarrier culture systems that offer the advantage of scale-up, minimizing contamination.

R subgroup (or side chain) The group of atoms that differs among different amino acid molecules and thus determines their diverse chemical properties; for example, the R subgroup on a Gly molecule is simply a hydrogen atom, on an Ala it is a methyl complex (a carbon atom and three hydrogens), and on Glu it is a combination of carbon, oxygen, nitrogen, and hydrogen atoms.

S

Saccharomyces cerevisiae Brewer's yeast, familiar to cooks as the yeast used to leaven bread, was the first and is still the most widely used yeast species in biotechnology. Certain strains are used in

the manufacture of alcoholic beverages and fermented foods—and also for expression of genes. Biologically active interferons, for example, have been produced in it and it can be used in the manufacture of biologics. Commonly abbreviated: *S. cerevisiae*.

scale-down To model a biopharmaceutical manufacturing process (or section of that process) at the laboratory scale, usually for validation or other study purposes. Scale-down requires holding the critical parameters constant, and may be confounded by differences in equipment dead volumes, performance, or materials of construction.

scale-up To transfer a biopharmaceutical manufacturing process from the laboratory scale to a manufacturing scale while holding critical parameters constant.

Schizosaccharomyces pombe The second most commonly used yeast species in biotechnology, originally used in east Africa to brew millet beer, but which is typically unsuitable for other types of fermentation because of the large amount of sulfurous compounds it emits.

SDMS *Scientific Data Management System*; an automated, electronic repository that stores and manages all types of scientific data to a centralized database, offering integration with a multitude of research applications.

SDS *Sodium dodecyl sulfate*; an ionic detergent that binds to and denatures proteins, and binds in rough proportion to the size of the protein; used to aid analytical separations.

SDS-PAGE *Sodium dodecyl sulfate-polyacrylamide gel electrophoresis*; the SDS detergent denatures and binds to proteins,

aiding in their separation. Analytical separation technique, often used to characterize proteins or mixtures, that uses a charged gel environment through which molecules of varying sizes and electric charges migrate from one pole to the other. Unlike gel-filtration chromatography, larger molecules move more slowly than smaller molecules because migration rate is not dependent on diffusion into and out of particles.

SEC *Size-exclusion chromatography*, gel-filtration or gel-permeation chromatography. An analytical method that uses porous particles to separate molecules of different sizes. Molecules that are smaller than the pore size can enter the particles and therefore have a longer path and longer transit time than larger molecules that cannot enter the particles. SEC can separate biological molecules and help scientists determine the molecular weights and molecular weight distributions of polymers.

SNP Single-nucleotide polymorphism (See DNA fingerprinting).

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.

seed stock The initial inoculum or the cells placed in growth medium from which other cells will grow.

sequence The precise order of bases in a nucleic acid or amino acids in a protein.

Ser *Serine*; one of more than 20 naturally occurring amino acids.

serum The watery portion of an animal or plant fluid (such as blood) remaining after coagulation.

shear Tearing force (to cells), such as that caused by blending or stirring.

shelf life The period of time during which a drug can be stored without decreasing in quality, safety, or efficacy.

sialylated oligosaccharides Oligosaccharides that contain sialic acid (N-acetyl) neuramic acid are sialylated). Sialic acid is often found as a terminal residue of oligosaccharide chains of glycoproteins. Sialic acid imparts negative charge to glycoproteins, because its carboxyl group tends to dissociate a proton at physiological pH.

silica Silicon dioxide, SiO₂, occurring naturally in crystalline, microcrystalline, and amorphous form; used to make glass and ceramics, and used in pharmaceuticals. Silica gel is a jelly-like form of silicon dioxide that is widely used as a solid medium, as a dehumidifying and dehydrating agent, and in many chemical processes.

SIP *Steam-in-place*; using steam to clean and sterilize equipment or systems without removing them from their installed location. (See CIP)

siRNA *Small interfering RNA, short interfering RNA, or silencing RNA*; a class of 20 to 25 nucleotide-long double-stranded RNA molecules that play a variety of roles in biology. Most notably, siRNA is involved in the RNA interference (RNAi) pathway, where it interferes with the expression of a specific gene. (See RNAi)

skid Common term for a complete chromatography system on wheels.

SMB *Simulated moving bed*; a method in liquid chromatography of making separations constant rather than in a batch process.

sodium hydroxide A highly caustic, alkaline chemical (NaOH) used to neutralize acids and destroy soft body tissues (with potassium hydroxide, the most widely used caustic agent in industry).

solubility The degree to which a solute can be dissolved in a defined solvent (sometimes describes the opposite of hydrophobicity).

solute A substance that is dissolved in a solvent; the part of a solution that is uniformly dispersed in another substance.

somatic cell In higher organisms, a cell that (unlike germ cells) carries the full genetic make-up of an organism.

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.

Southwestern blot Analytical blotting technique for studying DNA-protein interactions using labeled DNA to detect proteins transferred to membrane filters.

sparge To spray. A sparger is the component of a fermentor that sprays air into the broth.

species In chemistry, a particular kind of atomic nucleus, atom, molecule, or ion.

specifications Tests, analytical procedures, and appropriate acceptance criteria that are numerical limits or ranges that establish a set of criteria to which a raw material, drug substance, or drug product must conform to be considered acceptable for its intended use.

specificity The degree to which a substance exerts a definitive and distinctive

influence on a particular part of the body and on the course of a particular disease.

spectrometry Spectroscopy methods related to measurements of mass.

spectroscopy Study of the molecular absorption of light using optics. Different wavelengths and types of light can tell different things about the molecules' identity and condition. Proteins are often studied using fluorescence and infrared (see FT-IR) spectroscopy. Fluorescence spectroscopy induces molecules to emit light by the application of laser energy.

spike Adding a known amount of analyte from a laboratory standard, sometimes with something highly reactive (such as a radioactive or fluorescent dye) to act as a tracer. Used to check a method for recovery or accuracy.

sponsor Organization that takes primary ownership and responsibility for a product, and usually will be the license holder. A sponsor may outsource testing, clinical trials, or manufacturing to other entities (CLO, CRO, CMO) but retains oversight of the program. The exact division of roles is specified in contracts and in the quality agreement, a key GMP document.

spray-drying Creation of a fine powder by passing a bulk or final drug formulation through a hot air stream to evaporate dispersed droplets; contrast with freeze-drying.

stability 1. Ability to maintain constant characteristics in the presence of forces that threaten to disturb them; resistance to change. Resistance to structural, chemical, and biological changes in composition caused by such factors as light, temperature, and storage (shelf) time. 2. A defined char-

acteristic of a given product; stability profile means the types of chemical degradations, rates, and expected shelf life that characterize a product.

stabilizer A chemical additive that helps maintain solution stability or drug product stability.

staining A procedure of labeling tissues, organisms, or molecules (such as DNA or proteins) with colored or fluorescent dyes to allow visualization by microscopic or macroscopic techniques.

starting material European term meaning raw materials used in cGMP manufacturing, but excluding components. (See component, active starting material, raw material)

statistical process control Monitoring and controlling a process using statistical analysis with the aim of managing variability at critical process control steps.

stereoisomer Any of a group of isomers in which atoms are linked in the same order but differ in their spatial arrangement.

sterile Absolutely free of any microbiological contamination; an absolute state that cannot be proven unless all of a material is consumed in the test. In practical terms, sterility assurance is demonstrated by showing that less than 1 in 10^6 units may be contaminated. (See USP Sterility Test)

stoichiometry The study of proportional (quantitative) relationships between two or more substances during a chemical reaction.

strain A population of cells all descended from a single cell.

structural isomers Any isobaric species that has the same elemental composition (and assumed basic structure) but differs in the

arrangement of the elements, often assumed to be functional groups for biomolecules.

subcutaneous Referring to the layer of tissue (subcutis) directly underlying the cutis, which is mainly composed of adipose tissue. Subcutaneous (abbr: subq or sc) injections are given by injecting a fluid into the subcutis. It is relatively painless and an effective way to administer particular types of medication. Certain depot injections are a solid or oil-based medication, which is administered subcutaneously where it releases its agent slowly over a period of weeks.

sublimation Passing directly from a solid to a vapor state without first melting into a liquid.

substrate Reactive material, the substance on which an enzyme acts.

stratum The solid surface on which a cell moves or on which cells grow.

sulfation The formation of sulfuric acid esters from alcohols or olefins (synthetic fibers, such as polypropylene).

sulhydryl group Any compound of sulfur and another element, usually made by direct reaction of the elements.

supernatant Material floating on the surface of a liquid mixture (often the liquid component that has the lowest density); the overlying fluid layer that remains after precipitation of a solid component through centrifugation.

supercritical fluids Common gases, such as carbon dioxide, when under pressure contain a liquid form of the gas. This liquid is useful in a variety of biotechnology applications.

surface plasmon resonance A phenomenon used in analytical chemistry whereby

plasmons (electromagnetic waves formed by electrons) propagating along the surface of a thin metal layer resonate with light coming through a prism at a specific angle, stopping that light from reflecting. The electrical field thus created is very sensitive to chemical changes (such as molecular interactions) in a solution interfacing with the surface, which causes specific measurable differences in the angle of light necessary for the phenomenon to perpetuate. SPR biosensors detect and measure those changes.

surfactant Any substance that changes the nature of a surface, such as lowering the surface tension of water.

suspension Particles floating in (not necessarily on) a liquid medium, or the mix of particles and liquid itself.

sustained delivery Drug delivery in which the duration of release, action, and bioavailability are controlled and reproducible; usually a depot (reservoir) of drug is created in the body (at the injection site, for example), and the delivery matrix releases the therapeutic molecules over a period of time. Biodegradable polymers are under study as microspheres and other methods of sustained delivery for biomolecules.

symbiotic Living together for mutual benefit.

synthesis Creating products through chemical and enzymatic reactions. Bioprocessing lets living cells or organisms do this work.

T-U

tangential flow filtration A separation method that transfers components

of one system (stream) into another. The stream the product is being extracted from crosses the stream that the product is being transferred to multiple times.

target Organ, tissue, or molecule involved in a disease that is modified or affected by a potential therapeutic.

targeted delivery Drug delivery that is specifically directed to the therapeutic molecule's site of action by one of various means such as a targeting monoclonal antibody (that binds specifically to a particular kind of receptor) or surgery (in which a drug formulation is injected into a particular location, such as the liver).

T cell A synonym for T lymphocyte, T cells are a type of leukocyte (white cells of the blood and lymphoid system) that (along with the less numerous B lymphocytes in the bloodstream) are necessary for conferring antibody-independent cellular immunity. Of their subsets, cytotoxic or killer T cells can kill cells bearing specific antigens, helper T cells can help B cells form antibodies, and suppressor T cells suppress the activity of other cells involved in immune responses.

Team Biologics A partnership between FDA's Office of Regulatory Affairs (ORA) and CBER to focus on inspection and compliance issues in biologics. Its goal is to ensure the quality and safety of biologic products and resolve inconsistencies.

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

Thr *Threonine*; one of more than 20 naturally occurring amino acids.

thixotropy The property of some non-Newtonian pseudoplastic fluids to show a



In high-throughput laboratories, batches of samples are processed for screening, confirmation, or profiling purposes.

time-dependent change in viscosity.

throughput The movement of a material through a system; specifically, a measure of the quantity of a substance passing through a piece of equipment or section of a pipe or pump line during a specified time.

time-of-flight (TOF) mass spectrometer A mass analyzer that separates ions of different mass-to-charge ratios by their time of travel through a field-free vacuum region after having been give the same kinetic energy. The velocity of the ions is dependent on the mass-to-charge ratio and, as the ions are traveling over a fixed distance, the time taken to reach the detector allows the mass-to-charge ratios to be determined with heavier ions taking longer.

tissue culture Growing plant or animal tissues outside of the body, as in a nutrient medium in a laboratory; similar to cell culture, but cells are maintained in their structured, tissue form.

titer A measured sample. (To draw a measured, representative sample from a larger amount is to titrate.)

TOC analysis Total organic carbon

analysis; an analytical method whereby organic carbon is oxidized to produce CO₂, the amount of which produced is directly proportional to the amount of carbon present. Measurement of CO₂, as a result, indicates the presence of organic molecules. The biopharmaceutical industry uses TOC analysis to test pure water and to evaluate and validate cleaning procedures.

top-down sequencing The identification and characterization of intact protein from tandem mass spectrometry experiments, enabling the identification of post-translation modifications. The top-down approach provides direct measurement of the intact mass of the protein, as well as fragment ion information relating to the amino acid sequence.

toxicology Study of harmful substances: what they are composed of and which part is harmful, how they exert their effect, whether an antidote exists, and how the antidote works.

trade secret any unpatented and/or unpatentable trade-secret information and proprietary technology of any kind or nature owned by a company, such as a process method, formulation, or other information that adds value to a product or process.

TM *trajectory method*; The trajectory method treats the ion as a collection of atoms, each one represented by a 12-6-4 potential. The effective potential is obtained by summing over the individual atomic contributions; then trajectories are run in this potential to obtain the scattering angle (the angle between the incoming and departing buffer gas atom trajectory). The orientationally averaged collision integral is determined

by averaging over all possible collision geometries.

transcription Synthesis involving RNA polymerase of complementary RNA from a sequence of DNA.

transdermal delivery Drug delivery across the skin, accomplished without breaking the skin. For large molecules like proteins and peptides, this is possible only through iontophoresis.

transduction The transfer of genetic material from one cell or another by means of virus or phage vector.

transformation A change in the genetic structure of an organism by the incorporation of foreign DNA.

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 of the 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.

transmucosal delivery Drug delivery across mucosal membranes, such as the nasal lining, the inside of the mouth, or the rectal wall.

treatment IND An IND that makes a promising new drug available to desperately ill patients as early in the drug development process as possible. FDA permits the drug to be used if there is preliminary evidence of efficacy and it treats a serious or life-threatening disease, or if there is no comparable therapy available.

trehalose A sugar (non-reducing disaccharide) found in certain algae and plants, some bacteria, and some insects. It is used as a preservative and stabilizer in some biopharmaceutical formulations.

trend A statistical term referring to the direction or rate of change of a variable(s). [From ICH Q9]

trifluoroacetic acid A nonflammable, hygroscopic (takes up moisture), colorless liquid used as a reagent, solvent, catalyst, and strong nonoxidizing acid.

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.

Trp *Tryptophan*; one of more than 20 naturally occurring amino acids.

trypsin An enzyme capable of cleaving peptide bonds. It is used to remove adherent cells from a surface and to break up (digest) purified proteins for analysis.

tryptic fragment analysis Identifying and quantitating the peptides resulting from tryptic digestion.

TSE *Transmissible spongiform encephalopathies*; neurological disease in mammals

of many species, generally believed to be caused by prions.

turbidostat A variation on a chemostat. Whereas a chemostat is designed for constant input of medium, a turbidostat is designed to keep the organisms at a constant concentration. A turbidity sensor measures the concentration of organisms in the culture and adds additional medium when a preset value is exceeded.

turbulent flow field The state that results from mixing the contents of a fermentor or bioreactor to provide oxygen to the cells. That must be balanced against the shear that causes cell damage and death.

turnkey system A piece of equipment, process train, or manufacturing plant that is delivered to the customer in a ready-to-run condition, specialized for the customer's application, with no additional equipment or modifications required.

TWIG *travelling wave ion guide*; the mechanism by which mobility is implemented in an ion mobility capable mass spectrometer, i.e., Waters SYNAPT™ Systems. Ions are moved through a pressurized region by the action of a continuous train of transient voltage pulses, or travelling waves.

Tyr *Tyrosine*; one of more than 20 naturally occurring amino acids.

ultrafiltration Filtration under pressure.

undercooling An uncommon method of biomolecular preservation in which emulsions are used to cool the solution below its freezing point without freezing.

underflow The dewatered solids that result from compaction during centrifugation.

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.

unicellular A single-cell organism.

unit operation A distinct chemical or physical step in a downstream process, such as ultrafiltration, centrifugation, or chromatography.

UPLC® Technology The use of a high-efficiency LC system holistically designed by Waters Corporation to accommodate sub-2 µm particles and very high operating pressure is termed UltraPerformance Liquid Chromatography®. The major benefits of this technology are significant improvements in resolution over HPLC, and/or faster run times, while maintaining the resolution seen in an existing HPLC separation.

USP or USP-NF *The United States Pharmacopeial Convention, Inc.*; establishes and disseminates officially recognized standards of quality and authoritative information for the use in the manufacture and testing of drugs, excipients, and raw materials. Also called one of the compendia. Other compendia include, for example, *Ph.Eur (Pharmacopeia Europa)*, *JP (Japanese Pharmacopeia)*. The *USP*, which defined specifications for approved drugs as well as general methods and guidances, merged with the *NF, National Formulary*, which focused on specifications for raw materials and excipients. General chapters are not legally binding, but specific chapters are considered to be binding, and defined *USP* methods are accepted by the FDA as an appropriate standard.

USP sterility test A method defined in the *USP* and *Ph.Eur*, and considered acceptable for per-lot testing of parenteral

drugs to test for sterility. By itself, this test does not prove a given lot is sterile; rather, taken together with all other validation, GMP controls, and product/process testing, it increases confidence that a given lot is safe. (See sterility)

UV-vis *Ultraviolet-visible spectroscopy*; an analytical method that measures the absorption of light in the 200 to 750 nm range of the electromagnetic spectrum. It is used in determining protein concentration and is often applied to HPLC detection.

V-Z

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

vacuolation In cell and tissue culture, excess fluid, debris (aggregates), or gas (from sparging) can form inside a cell vacuole, a cavity within the cell that can be relatively clear and fluid filled, gas filled (as in a number of blue-green algae), or food filled (as in protozoa).

val *Valine*; one of more than 20 naturally occurring amino acids.

validation 1. Documented evidence that shows that an assay or process, when operated within specified ranges of critical parameters, has a high probability of meeting specifications. 2. The process of determining the degree of validity; the procedures involved in checking data for correctness, compliance with standards, and conformance with the requirement specifications. A series of experiments performed using a pre-ap-

proved protocol that will generate adequate documented evidence to support a claim of a validated state.

vCJD *Variant Creutzfeldt-Jakob disease*; a fatal neurological disease in humans, believed to be caused by infection with a prion that also causes bovine spongiform encephalopathy (BSE) or “mad cow disease” in cattle. CJD, or classical CJD, is not caused by the BSE agent, and its etiology is unknown.

vector The plasmid, virus, or other vehicle used to carry recombinant DNA into the cell of another species.

venture capital Also risk capital; money invested in a small, young, or start-up company that is perceived to have excellent growth prospects but without other access to capital markets. Venture capitalists generally supply capital in return for substantial equity and/or a seat on the board of directors. Sometimes, they provide management and other financial support to their investee companies.

Vero An established cell line derived from the kidney of the African green monkey.

vessel jacket A temperature control method consisting of a double wall outside the main vessel wall. Liquid or steam flows through the jacket to heat (or cool) the fluid in the vessel. Because biopharmaceutical products are so sensitive and vessel jackets can cause uneven heating (hot or cold spots), shell-and-tube or plate-and-frame heat exchangers are more common in biopharmaceutical production systems.

viability The extent to which cells and tissues are living. Cells can be metabolically viable even if they are not reproductively viable.

viral clearance step Process step which separates a given class of virus, if any are present, from the desired product. A clearance factor may be estimated by performing scaled-down experiments using a model virus, to determine process capability.

viral inactivation step Process step, which inactivates the activity of a given class of virus to provide assurance of safety. An inactivation factor may be estimated by performing scaled-down experiments using a model virus, to determine process capability.

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 to 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.

virus-like particles Also RVLP (retrovirus-like particles); particles that resemble retroviruses, yet lack infectivity, and usually are found in established lines of mammalian cells. Cell bank characterization seeks to determine whether viral activity is present, as a means of assessing risk. Not present in nonmammalian cells or cell lines.

viscosity Thickness of a liquid; determines its internal resistance to shear forces.

warning letter The most serious FDA post-audit (after inspection) letter, notifying a manufacturer of adverse inspection findings and giving it 15 days to reply with a concrete plan for remediation. May or may not be associated with other actions, such as injunction, consent decree, or product seizure.

washing (of a column) Flushing a column with a large volume of a solvent or buffering agent before selective elution of the desired analyte.

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.

Western blot An immunochemical method for identifying proteins in a complex mixture, proteins separated by electrophoresis are transferred (blotted) from the gel medium to a protein-binding nitrocellulose or polymeric membrane; the transferred proteins are then detected by their relative binding to labeled antibodies. (See blotting)

WFI *Water for injection*; very pure water that meets specifications defined by the USP or other compendia; suitable for parenteral uses.

withdrawal Product withdrawal; a recall of a lot of product that is done voluntarily by a firm, when there is concern about product quality that is not proven. A recall may be mandated by FDA or regulatory bodies. (See also recall)

WHO *The World Health Organization*; a United Nations organization.

working cell bank A cell bank that

is usually made from a single vial of the master cell bank, in which each vial has comparable contents and is expected to perform consistently when introduced into a process or assay. Both master and working cell banks are extensively tested and characterized before use. Manufacturing usually starts when a vial of working cell bank is thawed and added to a reactor. (See master cell bank)

xenobiotic A chemical found in an organism but which is not normally produced or expected to be present in it. It can also cover substances which are present in much higher concentrations than are usual. Specifically, drugs such as antibiotics are xenobiotics in humans because the human body does not produce them itself, nor are they part of a normal diet.

xenotransplantation Implantation of living cells, tissues, or solid organs from one species into another, used when human donors are unavailable or when a temporary or “bridge” organ is needed; a controversial practice given concerns about potential viral transmission and strong immunological reactions.

YAC *Yeast artificial chromosome*; a vector used to clone DNA fragments up to 100,000 base-pairs long. YACs are constructed from the telomeric, centromeric, and replication sequences of yeast cells.

yeast A single-celled fungus (eukaryote).

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suggested resources

If you are looking for additional information (or terms not included in our glossary), here are some places to begin your search.

BOOKS

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Expediting Drug and Biologics Development: A Strategic Approach, 3rd ed., Steven E. Linberg, Ed. (Parexel International Corporation, Waltham, MA 2006)

FDA-Speak: A Glossary and Agency Guide, 2nd ed. D.E. Snyder, Ed. (CRC Press, Boca Raton, FL 2001)

Handbook of Biopharma Industry Acronyms & Terms, Ronald P. Even, Ed, (Jones and Bartlett Publishers, Sudbury, MA 2009)

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ORGANIZATIONS

American Association of Pharmaceutical Scientists, Arlington, VA
aaps.org

Biotechnology Industry Organization
Washington, DC; bio.org

California Separation Science Society
San Francisco, CA
casss.org

FDA
US Food and Drug Administration
Rockville, Maryland
Center for Biologics Evaluation and Research,
www.fda.gov/cber/index.html
Center for Drug Evaluation and Research,
www.fda.gov/cder
Electronic Freedom-of-Information Reading
Room, www.fda.gov/foi/

Health Canada
Health Products and Food
Branch Inspectorate, Ottawa, ON
hc-sc.gc.ca

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
Geneva, Switzerland
ich.org

International Pharmaceutical Excipient Council of the Americas
Arlington, VA
ipeamericas.org

International Society for Pharmaceutical Engineering

Tampa, FL
 ispe.org

National Center for Biotechnology Information

National Library of Medicine
 Bethesda, MD
 ncbi.nlm.nih.gov

Parenteral Drug Association

Bethesda, MD
 pda.org

WORLDWIDE WEB SITES

www.antibodyresource.com
 The Antibody Resource Page

www.biotechinstitute.org
 The Biotechnology Institute

www.online-medical-dictionary.org
 The Online Medical Dictionary

whatis.techtarget.com
 TechTarget's glossary of IT-related words

www.nationalhealthmuseum.org
 The National Health Museum online

www.biospace.com
 BioSpace

www.bioworld.com
 BioWorld Online

www.chem.vt.edu/chem-ed/ac-meths.html
 Encyclopedia of Analytical Instrumentation from the Virginia Tech's Chemistry Hypermedia Project

www.emea.europa.eu
 European Medicines Agency

www.gened.com/glossary/index.html
 GeneEd's biotechnology glossary

www.genomicglossaries.com
 Genomics Glossary by Cambridge Healthtech Institute

ifpma.org
 International Federation of Pharmaceutical

Manufacturers & Associations

www.inpharm.com
 InPharm

www.intelihealth.com
 Aetna IntelliHealth

www.medicinenet.com/Script/Main/hp.asp
 MedicineNet.com. See Med Term dictionary from the home page

www.medscape.com
 MedScape

www.bioethics.upenn.edu
 Bioethics.Net

www.merck.com/pubs
 Merck publications online (searchable)

users.path.ox.ac.uk/~scobbold/tig/new1/mabth.html
 "A Hundred Years of Antibody Therapy"

www.mtdesk.com
 Alphabetical index of terminology: new drugs, equipment, and procedures

www.ncbi.nlm.nih.gov
 NCBI's PubMed

www.genome.gov
 Glossary of Genetic Terms from the National Human Genome Research Institute's division of intramural research

www.ornl.gov/TechResources/Human_Genome/glossary
 Human Genome Project's genome glossary

www.pharma-lexicon.com/index.php
 MediLexicon

www.ncbi.nlm.nih.gov
 National Center for Biotechnology Information

www.pdr.net
 PDR.Net

www.expasy.org
 Swiss Institute of Bioinformatics

www.webmd.com
 Web MD

www.whymbiotech.com
 Council for Biotechnology Information

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