



Graver Technologies

Technical Brief

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Glossary of Biotechnology Terms

Every industry has an abundance of terms that may be used to describe products and processes. Because of the critical nature of the pharmaceutical and biotechnology markets and the fact that it is highly regulated, it is critical to define and understand some of the more common terms.

Acholeplasma laidlawii

One type of Mycoplasma (microorganism) used as the target organism for sterility testing of $\leq 0.1 \mu$ membrane filters.

Aerobic

Microorganisms which grow in the presence of oxygen.

Anaerobic

Microorganisms which do not require oxygen to grow and for which oxygen may be toxic. Literally means "life without air."

Anion

A negatively charged particle. If a surface has a positive charge it is called anionic because it can be used to capture negatively charged molecules.

Antibiotic

A chemical substance derivable from a mold, bacterium or synthesized that can kill microorganisms.

Antibodies

Antibodies are proteins (immunoglobulins) synthesized by the immune system in response to an antigen and play an important role in the body's defense against infection. They have a unique shape that enables them to interact specifically with the antigen.

Antigen

A foreign substance (a protein or high molecular weight polysaccharide) which results in the formation of antibodies. Examples are bacteria, viruses, pollen and vaccines.

API

Active Pharmaceutical Ingredient

Aseptic

Refers to a process performed in a sterile or controlled environment using appropriate precautions (such as flaming pipettes) designed to prevent contamination through introduction of microorganisms.

ASTM 838-05

Standard Test Method for Determining Bacterial Retention Of Membrane Filters Utilized For Liquid Filtration. This original test method used to determine the bacterial retention characteristics of membrane filters for liquid filtration using *Brevundimonas diminuta* as the challenge organism.

Autoclave

An instrument used to sterilize equipment and supplies by subjecting them to high pressure saturated steam at 121°C for around 15–30 minutes.

Bacteria

Single-celled or non-cellular spherical, spiral or rod-shaped organisms lacking chlorophyll that reproduce by cell division (fission).

Bactericide

A substance which destroys bacteria.

Bacteriophage

A virus that exclusively infects bacteria.

Bioburden

The level of microorganisms typically measured as colony forming units (CFU) in a substance to be filtered.

Biomass

The total weight of living matter present in a specific area.

Bioreactor

A vessel, usually stainless steel or glass, used for growing mammalian, bacterial, or plant cells. A fermentor.

Brevundimonas diminuta

A rod shaped bacteria used to rate the efficiency of 0.2 micron sterilizing filters during validation testing Prior to reclassification, it was known as Pseudomonas diminuta. Sterilizing filters must retain a challenge of this organism under challenge conditions (10^7 cfu/cm²).

Cation

A positively charged particle. If a surface has a negative charge it is called cationic because it can be used to capture positively charged molecules.

CBER (Center for Biologics Evaluation and Research)

Part of the FDA concerned with biologic drugs, particularly with the new protein and peptide drugs developing from biotechnology.

CDER (Center for Drug Evaluation and Research)

Part of the FDA concerned with all small volume parenterals (SVP's), large volume parenterals (LVP's) and non-biological drugs.

Cell Culture

The growth of cells in a vessel such as a flask, spinner bottle, or bioreactor. It is typically used to produce large quantities of cells which express recombinant proteins. Microfiltration is used to sterilize the media and growth enhancers added to media.

cGMP – Current Good Manufacturing Practices

Regulations that describe the methods, equipment, facilities, and controls required for producing: Human pharmaceutical products and veterinary products (21 CFR 210-211); Biologically derived products (21 CFR 600 and 21 CFR 620); Medical devices (21 CFR 820); Processed food (21 CFR 100).

CIP - Clean in Place

A method of cleaning the interior surfaces of pipes, vessels, process equipment, filters and associated fittings, without disassembly by delivering highly turbulent, high flow-rate solution (applies to pipe circuits and some filled equipment); delivering solution as a low-energy spray to fully wet the surface (applies to lightly soiled vessels where a static sprayball may be used); delivering a high energy impinging spray (applies to highly soiled or large diameter vessels where a dynamic spray device may be used). In addition, elevated temperature and chemical detergents are often employed to enhance cleaning effectiveness.

Clinical Trials

Required testing as part of drug development to study the safety and efficacy of new drugs in human subjects prior to the drug's approval by the FDA.

Cold Sterilization

Removal of all bacteria by filtration through a sterilizing grade 0.2 μ filter.

Colony Forming Unit

A measure of viable bacterial or fungal numbers. The results are given as CFU/mL (colony-forming units per milliliter) for liquids or CFU/g (colony-forming units per gram) for solids.

Cytotoxic

Substance that is toxic to cells or is cell-killing.

Cytotoxicity Test

Part of USP Class VI testing designed to determine the biological reactivity of mammalian cell cultures following contact with specific extracts prepared from the material under test

DMF (Drug Master File)

A document submitted to the FDA that explains the formulation of an active ingredient or component of the manufacturing process and is referenced in an Investigational New Drug (IND), New Drug Application (NDA), or Amendment to New Drug Application (ANDA) from a company.

E. coli (Escherichia coli)

A bacterium commonly used in recombinant DNA technology. Occurs naturally in the human intestine.

Endotoxin

A structural component (lipopolysaccharide) of the cell wall of gram negative bacteria. When the integrity of the wall is disturbed, through cell division, growth and death, endotoxins may be released into the product. Endotoxins must be controlled in parenteral products as they may result in a fever reaction in mammalian systems.

FDA

U.S. Food and Drug Administration.

Fermentation

The process of growing microorganisms within an enclosed tank (fermentor) under controlled conditions. It is necessary to provide aeration, and agitation as well as control temperature, pH, and carbon/nitrogen sources.

Generic Drug

A drug product produced and marketed under its chemical or common name after a proprietary drug goes off patent (17 years). Generic drugs are typically less expensive but must still meet the stringent standards as specified by the FDA.

Gram Stain

A basic technique used for the classification of bacteria where an organism that retains a crystal violet stain is considered gram positive and organisms that exhibit only the counterstain are gram negative.

Heat Labile

Pharmaceuticals that are able to be destroyed by high temperature and must be sterilized by filtration.

In Situ

Sterilization or integrity testing of a filter in the system rather than removing it and performing the operation in an autoclave or separate integrity test stand. Derived from Latin meaning "in place".

In Vitro

An experiment performed outside or isolated from the living organism. Literally means "in glass".

In Vivo

An experiment performed using a living organism. Literally means "in life".

Integrity Test

A test to ensure that a filter is intact and will function to the standards established by the manufacturer. There are three typical integrity tests used : Forward Flow Test (diffusive flow) , Bubble Point test, and the Pressure Hold test. Integrity tests on sterilizing grade filters are correlated with bacterial challenge data.

Intermediate

An organic compound that is formed in a stage of production of an active pharmaceutical ingredient. It is often the active portion (see API) of the final drug product or a critical component of in the pathway to the final product.

LAL (Limulus Amoebocyte Lysate Test)

A test prescribed by the United States Pharmacopeia (U.S.P.) to detect and determine the level of bacterial endotoxins in a substance. The reagent is made from the circulating blood cells (amoebocytes) of the horseshoe crab (*Limulus polyphemus*).

Lipids

Any numerous fats and fat-like materials that are insoluble in water but are soluble in common organic solvents.

Log Reduction

The logarithm to the base 10 of the ratio of organisms in the feed to the organisms in the filtrate. In simplest terms, a log reduction means a ten-fold reduction and is reported as LRV (log reduction value).

LVP (Large Volume Parenteral)

A category of intravenous drug products packaged in containers of 100 - 1000 mL. Typically used to correct electrolytic imbalances, replace body fluid and provide general nutrition and are given to a patient over an extended period of time.

Lysis/Lyse

Destruction of a cell and the release of its contents by disrupting the cell wall by using various agents such as detergents or enzymes. It is often necessary in fermentation processes that produce intracellular recombinant proteins.

Microbe /Microorganisms

Typically refers to single-celled organisms such as bacteria, protozoans, yeast, viruses or algae.

Mycoplasma

A class of microorganisms without cell walls and are deformable. They have been shown to be capable of penetrating a 0.2 micron sterilizing grade membrane and require a 0.1 micron for complete retention.

NDA (New Drug Application)

New Drug Application. Filed with the FDA and after approval, allows a company to begin to distribute and market a new drug. Must have completed product validation and all clinical trials.

NF (National Formulary)

A compendium of purity and testing criteria for chemicals and usually published in combination with the USP.

Nutraceuticals

A composite of food and pharmaceuticals. A class of foodstuff (as a fortified food or dietary supplement) that provides health benefits.

NVR (Aqueous extractable)

A standard test method for determining residue on evaporation in a solvent extract from a component using a rotary flash evaporator.

Parenteral Drug (LVP, SVP)

A drug that is infused (IV) or injected (IM or subcutaneous) into the human body.

Purified Water, USP

A pharmaceutical grade of water produced by distillation, reverse osmosis or deionization. Typical uses are to rinse equipment, vials and ampoules, and as base for cosmetics and oral drugs. It is not used as raw material for parental drugs.

Pyrogen

See endotoxin

Saccharomyces cerevisiae (Baker's Yeast)

A strain of yeast used in fermentation of wines and beers and during the validation of 0.65 micron membrane filters.

Sanitization, Sanitize

A process to make sanitary or hygienic in order to reduce the possibility of growth and spread of pathogenic organisms. Common sanitization agents include bleach, peracetic acid and hydrogen peroxide.

Serratia marcescens

A bacterium used for defining and validating 0.45 micron removal rated filters.

Sterile Water for Injection, USP

Same as WFI, but sterile packaged.

Sterilize

A process that eliminates or kills all forms of microbial life including fungi, bacteria and viruses that can be present on a surface, contained in a fluid or in pharmaceutical preparations, or in a compound such as biological culture media. Sterilization can be achieved by applying the combinations of heat, chemicals, irradiation, high pressure, and filtration.

Sterilizing Filter

A filter that produces an effluent in which no microorganisms are demonstrable when tested by the method specified in the current edition of the United States Pharmacopoeia. The filter is challenged with a specified microorganism at $10^7/\text{cm}^2$. Usually accepted as 0.2 μm absolute pore-size rating.

SVP (Small Volume Parenteral)

A category of intravenous drug products packaged in containers of less than 100ml. Typically administered to a patient in a single syringe injection.

Titer Reduction

Titer reduction is calculated by:

$$T_R = \frac{\text{Total number of CFU influent to the filter}}{\text{Total number of CFU effluent to the filter}}$$

Alternative nomenclature to Log Reduction Value (LRV)

USP (United States Pharmacopeia)

A compendium of testing and purity criteria for pharmaceuticals and raw materials. Recognized and accepted as the standard reference guide by FDA and other regulatory agencies.

Vaccine

A preparation of microbial antigens that is injected and which stimulates the production of antibodies, creating immunity for the recipient. They may contain material from a non-virulent organism which retains its immunogenicity but does not result in infection; contain a modified toxin which has lost its toxic properties but retains its ability to create an immune response.; or contain live, attenuated (weakened) organisms which are similar to the original strain but lack virulence.

Validation

A process or product that has been demonstrated to perform as specified, and does so reproducibly with safety, efficiency, accuracy, and precision.

Vent Filter

A filter intended to separate the liquid contents of a vessel (tank, fermentor, bioreactor) as well as its vapors and gas from the ambient air. Prevents the passage of microorganisms and liquid while allowing the passage of gases. Best accomplished by the use of hydrophobic media such as PTFE.

Virus

Simple life form that invades living cells and uses their chemical machinery to keep itself alive and to replicate itself.

Water Intrusion Test (WIT)

An in-situ integrity test for hydrophobic filters. The WIT measures the decay rate of a pressure level imposed upon a hydrophobic membrane enveloped in water.

WFI (Water-For-Injection, USP)

Water purified by distillation or reverse osmosis and containing no added substances. It must meet the purity requirements for USP Purified Water with a pH between 5 and 7, total dissolved solids (TDS) less than 10 ppm, passes USP test for oxidizables and pass the USP endotoxin test.

Yeast

Any of various unicellular fungi of the genus *Saccharomyces*.