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Volume 8 • Issue 1

Production Insight

Solutions for Critical Environments & Manufacturing Processes

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SPECIAL EDITION

Special Edition Issue Featuring a Collection of Recent Articles

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Delivering Effective Solutions Through Collaboration

As a leading, global provider of product and service solutions for traditional pharmaceutical production, bioprocessing, as well as fabrication of medical devices and microelectronics, VWR understands the various challenges often encountered in manufacturing environments.

Whether those challenges have stemmed from stringent product or process requirements, secondary sourcing options, supply chain security considerations, or the need for support services to increase productivity, we can deliver innovative and impactful solutions from discovery to delivery by partnering together.

In this issue, you'll find a collection of articles that address several current production environment topics with unique solutions that have proven to be successful.

Super Refined® Polysorbates for High-Demanding Formulation Applications

By W. Hesselink, Application Project Manager, Avantor

Eliminating impurities in drug formulations has always been a key focus for pharmaceutical manufacturers. The reason is simple – impurities can reduce the efficacy of active pharmaceutical ingredients (APIs) in formulations.

Today, pharmaceutical manufacturers are working with new APIs that are much more effective in formulations, but increasingly prone to stability issues and more sensitive to impurities. As a result, formulators are looking to their suppliers to find ways to reduce impurities and enhance API efficacy. In response, polysorbate products created with an advanced process can reduce impurities down to levels not previously achieved with traditional polysorbates.

Introduction to polysorbates

Biopharmaceutical formulators often used polysorbates for the benefits they provide in parenteral dosage applications (injectable, intravenous, subcutaneous), although these excipients are also used in solid and liquid dosage form products for their positive contribution to stability and API effectiveness.

Composed of fatty acid esters of polyoxyethylene sorbitan, polysorbates are surfactants which are amphiphilic and non-ionic. The largest fatty acid component dictates the general type of polysorbate. Polysorbate 20 is based on lauric acid, while polysorbate 80 is based on oleic acid. These structures provide high hydrophilic-lipophilic balance (HLB) numbers and low critical micelle concentration values, the factors responsible for their common use in drug formulations. The choice between polysorbate types depends on their specific interaction with APIs or other excipients. Polysorbate 80 is one of the most common surfactants currently used in formulation of protein biopharmaceuticals.

Stability of polysorbates

High-purity J.T.Baker® brand polysorbates are vegetable-based, with a non-peanut origin, providing low endotoxin and other impurities. These high-purity materials can provide robust formulation by improving oxidative stability and shelf life (see Fig. 1 on next page). The low endotoxin and peroxide level is critical for formulation of biopharmaceuticals.

Applications of polysorbates

Polysorbates are used in a variety of biotechnology and small molecule drug formulations to improve solubilization and stability. The surface activity of polysorbates serves to stabilize proteins, by reducing the alteration or aggregation of proteins during manufacturing, distribution and storage.

When formulated with poorly soluble drugs, polysorbates provide improvements in solubilization. In addition, the enhanced stability of emulsions with polysorbates is widely known.

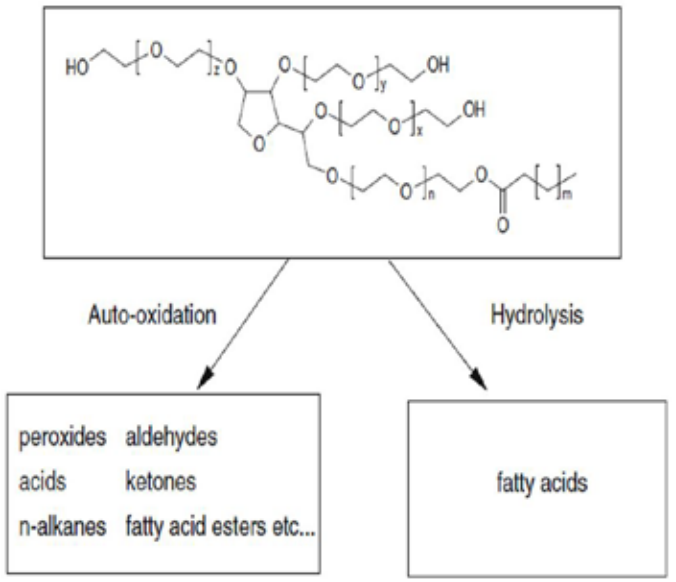


Fig. 1- PS 80 can degrade by auto-oxidation of polyoxyethylene chain hydrolysis of fatty acid ester bond

cGMP manufactured polysorbates meet multicompendial requirements

With state-of-the-art cGMP subdivision processes in FDA-registered ISO 9000-certified facilities, Avantor offers polysorbates in a variety of container sizes, packaged under nitrogen to ensure premium product integrity. These products meet the rigorous multicompendial requirements of the National Formulary (NF), European Pharmacopoeia (EP) and Japanese Pharmacopoeia (JP) or Japanese Pharmaceutical Excipients (JPE).

These polysorbates are GRAS listed and accepted as food additives in Europe, and are included in the FDA Inactive Ingredients Database (for IM, IV, oral, ophthalmic, otic, rectal, topical, and vaginal preparations) and the Canadian Natural Health Products Ingredients Database. In addition, they are suitable for manufacturing parenteral dosage forms and are included in parenteral and non-parenteral medicines licensed in the UK.

Super Refined® (SR) polysorbates for demanding drug formulations

While high-purity grade polysorbates offer low levels of impurities to ensure high performance in formulations, a proprietary flash chromatographic process used to make Super Refined® (SR) polysorbates has been shown to remove even more polar and oxidative impurities, such as peroxides and aldehydes, that can degrade APIs, and color (Fig. 2). The decreased level of these impurities helps maintain API integrity and stability in formulations like parenteral drugs involving monoclonal antibodies or recombinant proteins (such as certain cancer drugs), and other formulations in suspension or emulsion dosage form.

Fig. 2 - Super Refining process (left) removes color and oxidative impurities

Avantor offers the two most widely used types of polysorbates—polysorbate 20 and polysorbate 80—under its J.T.Baker® brand. Each type is available in both high-purity and Super Refined® grades, manufactured under cGMP conditions. The different grades have different specifications.

Examples of Super Refined® polysorbate formulations include, but are not limited to intramuscular (IM) and intravenous (IV) injections, ophthalmic preparations, oral capsules, solutions, syrups and tablets, topical, vaginal and rectal preparations.

Effect of polysorbate 80 quality on photostability of a monoclonal antibody

When traditional polysorbate 80 aqueous solutions are exposed to light this can result in peroxide generation, which in turn may result in oxidation of the susceptible amino acid residues in the protein molecule. In a study[2] published in 2012 by ImClone Systems, a subsidiary of Eli Lilly, a proprietary monoclonal formulation with 0.01% PS 80 was exposed to high light vs. dark controls. The purpose of this study was to determine if the photostability of a proprietary IgG[1] monoclonal antibody formulation containing polysorbate 80 is affected by the quality (grade/vendor) of the polysorbate 80 ingredient.

The study concluded that Super Refined® polysorbate 80 improves the photostability of a proprietary IgG[1] monoclonal antibody. The J.T.Baker® Super Refined® polysorbate 80 vs. the polysorbates of EMD and NOF shows higher polysorbate monomer retention and lower formation of degradants (low Mw species); lower formation of aggregates (high Mw species); and a lower degree of oxidation of four different peptide fragments in high light-exposed formulations (Fig. 3). The low levels of peroxide impurities found in polysorbate 80 may facilitate oxidative degradation of the protein. This might be particularly significant with regards to the photostability of the formulation.

Super Refined® polysorbate 80 reduces stresses on cell membranes

The human cell membrane is susceptible to oxidation stresses, particularly peroxides and carbonyls, which cause cellular disruption, and ultimately irritation. Super Refining removes these stresses from polysorbate. Formaldehyde is a known irritant to the cell membrane. Fig. 4 demonstrates how Super Refined® polysorbate 80 reduces the levels of formaldehyde compared with the standard compendial grade[3].

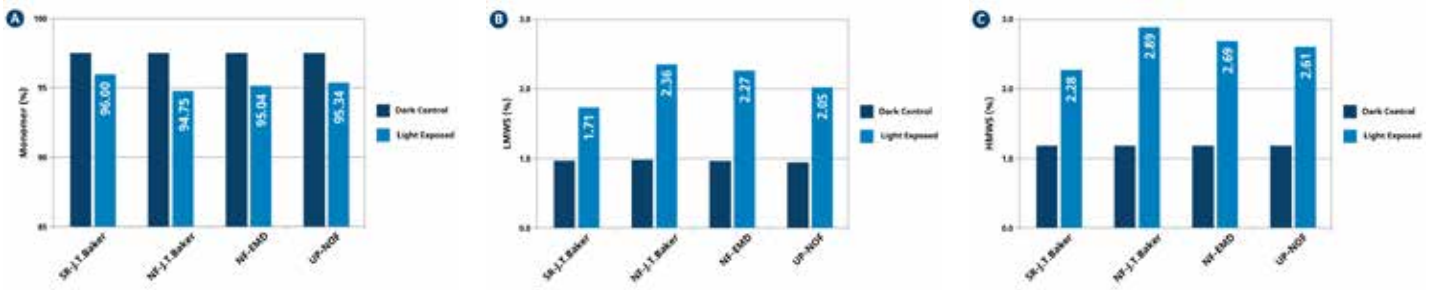


Fig. 3 - Percent monomer, degradants and aggregates in dark controls and light-exposed samples for various groups of formulations.
A) percent monomer B) percent degradant and C) percent aggregate in dark control and light-exposed samples.

Application and customer needs for Super Refined® polysorbates

Polysorbates 20 and 80 are used in the formulation of biotherapeutic products, for example preventing surface adsorption and as stabilizers against protein aggregation. In some cases, and depending on the application it is sometimes necessary to use the Super Refined® polysorbate because this product has been purified to reduce some impurities that can cause unwanted reactions, or aggregation of the API.

Conclusion

The super refining process to purify polysorbates significantly reduces the color, polar and oxidative impurities such as peroxides and aldehydes that can degrade APIs, making it the ideal excipient when formulating with sensitive and unstable protein actives, or when color and odor control is crucial for the formulation. With our offering of Super Refined® polysorbate products, we make it possible for customers to match the right level of purity to their specific API needs. This is especially relevant to makers of critical parenteral formulations including the growing biosimilars market. The purity of polysorbates should be considered as a critical quality attribute in the design and development of sensitive protein drug formulation and contributes to overall improved safety, and pharmacological activity of the formulated API.

[1]Source: http://www.ema.europa.eu/ema
[2]Source: Singh et al, AAPS PharmSciTech (13), 2012
[3]Source: Internal investigation of original manufacturer
*Super Refined® is a registered trademark of Croda Inc.

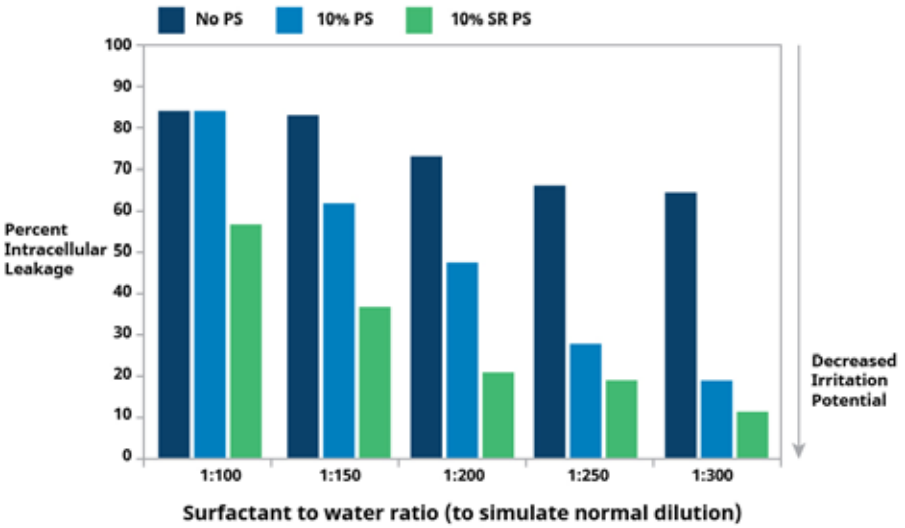


Fig. 4 - Trans-epithelial (TEP) assay with three formulations that contain different grades of polysorbate 80

Enhancing Cleanroom Quality Control and Efficiency through Direct Dispense Technology

By Nandu Deorkar, Ph.D.
Vice President of Research and Development, Avantor

Biopharmaceutical manufacturing is a complex process that involves acquiring, storing and using precise amounts of materials, many of which are dry powders packaged and shipped from suppliers in bulk amounts. These materials are typically handled by trained personnel in cleanroom packaging suites following strict protocols to prevent cross-contamination and ensure consistent product quality.

Preparing buffer and cell culture materials in a cleanroom setting can be labor-intensive and requires substantial investment in facilities and resources, as well as repeated quality assurance testing as bulk materials are subdivided for individual process runs. In addition, time-consuming cleaning and sterilization is required between each batch of materials being processed.

New innovations in raw materials packaging can directly improve this process. Avantor's J.T.Baker® Direct Dispense packaging technology provides single-use, pre-weighed free-flowing delivery of products such as salts, buffers and other cell culture materials directly into production equipment. Materials delivered through the Direct Dispense system can essentially bypass the cleanroom – providing ways to make cleanroom operations more flexible and less of a potential "bottleneck".

Cleanrooms are Labor-Intensive

While pharmaceutical and biopharmaceutical producers are focused on quality, safety and drug efficacy, they are also continuously challenged to reduce costs and improve manufacturing efficiencies. One target for improvement is the cleanroom packaging operation, a necessary but labor-intensive process that can impede production flexibility and throughput.

Upstream biopharmaceutical processes consume raw materials such as cell culture media, carbohydrates, amino acids and buffers, typically supplied in powder form. The bioreactors and medium preparation tanks using these materials often operate around the clock: large-scale reactors with 10,000 L capacity can run continuously up to 35 days, while newer generation single-use production systems, with multiple 2,000 L bioreactors are often configured to operate in overlapping sequences to achieve similar or greater productivity.

Until recently, it was common for most of these materials to be delivered in bulk amounts from suppliers, either in 100 kg drums with one or two plastic liners, or smaller cardboard boxes with plastic liners holding 50 kg. These bulk materials end up making at least two (and sometimes up to five) trips through the cleanroom packaging suite:

- Initial receipt: To receive the material upon the shipment arrival, it needs to be sampled and properly identified. The bulk container is brought into a cleanroom packaging suite and opened to sample. This independently confirms via lab analysis that the quality, purity and characterization match what was ordered. The bulk container is then closed and properly resealed for transport to the warehouse for later use. Some manufacturers also choose to take extra samples for additional characterization tests or future reference.
- Subdivision: Once the material is ready for use, the container is brought back to the cleanroom environment where the appropriate amount is weighed and dispensed into interim packaging. If any material is unused from the original container, it often goes back to storage until needed and the subdivision process in the cleanroom is repeated.

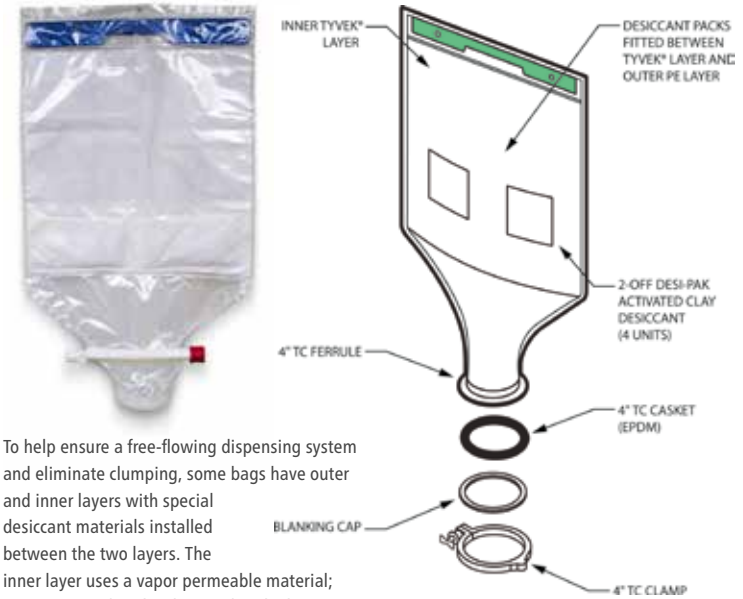
Both the sampling upon receipt and the multiple subdivision steps all make use of the cleanroom and its personnel; for a 2,000 L bioreactor, a manufacturer may need to subdivide a 100 kg drum of material between two and five times.

Cleanroom Processes

Cleanroom facilities and personnel are some of the most tightly scheduled resources in the biopharmaceutical production environment. Given the round-the-clock operations at these companies, manufacturers need to strike an extremely careful balance between stringent quality control and improving efficiency.

Consider the basic steps involved in conducting a standard subdivision of buffer materials:

- The bulk container exterior is typically cleaned of any particulates and brought into the cleanroom by fully gowned personnel. This is typically done one container at a time, to eliminate cross-contamination risks.
- Proper, step-by-step procedures need to be followed for opening each bulk container, hand-separating and weighing the material to be delivered to production.
- Since the bulk container is open throughout subdivision, some biopharmaceutical producers conduct multiple lab analyses of these drums, each time a new quantity of material is removed, to confirm that no issues have occurred.
- All devices and gloves used must fully comply with the cleanliness demands of the cleanroom and the work undertaken in the cleanroom. They must be cleaned, disinfected, or sterilized as appropriate for



To help ensure a free-flowing dispensing system and eliminate clumping, some bags have outer and inner layers with special desiccant materials installed between the two layers. The inner layer uses a vapor permeable material; any moisture that develops within the bag passes through this material and is controlled by the desiccant, to maintain the correct moisture levels.

the type of work being done and the risk they pose for contamination.

- Once subdivision is complete, both the bulk material container and the container holding the production buffers must be sealed and the exteriors sanitized once more before they are delivered to the warehouse or the bioreactors.
- Once this material is removed, full decontamination procedures need to be followed before the next material for subdivision is brought into the cleanroom packaging suite. And when changing materials, the personnel must exit the cleanroom and change gowns, masks and gloves before beginning the next subdivision process.

Some raw materials such as salts, buffers, amino acids and carbohydrates, have an intrinsic propensity to form clumps or cake in storage. Breaking up these clumps is an additional, time-consuming step that cleanroom personnel must complete to measure out the precise amounts needed for bioreactor processes.

All these procedures must be carefully documented according to cGMP standards. The personnel in cleanroom packaging suites need to be highly trained, since working in clean environments demands knowledge, discipline and motivation, as well as a thorough understanding of contamination risks among all personnel involved.

Direct Dispense Enables new Flexibility

Managing the flow of materials through these cleanroom packaging suites is a constant challenge. Avantor's J.T.Baker® Direct Dispense packaging technology offers ways to help streamline cleanroom operations, reduce risks and eliminate the potential for production bottlenecks.

This packaging option provides single-use, pre-weighed and free-flowing product in specially designed, transparent polymer bags that are available to pack up to 100 kg of material. These bags dispense salts, buffers and other cell culture materials directly into their media or buffer preparation tanks, in the exact amounts specified for a given process.

Materials in Direct Dispense packaging do not need to be processed through cleanroom packaging suites: They can be received directly into inventory, and then delivered to production as needed. While many products will still be supplied in bulk containers (requiring sampling upon receipt and then subdivision as needed), incorporating use of Direct Dispense packaging can "lighten the load" on cleanroom suites, enabling more flexibility in using these facilities.

The size, shape, sealing and seams of these bags are designed so that when they are inverted, they dispense virtually all the pre-weighed material into the bioreactor. An important consideration here is that pre-weighed and dispensing amounts are within a one-percent tolerance of the amount of material required. In addition, Direct Dispense bag systems are compatible with non-destructive identity-testing tools, such as contact-free Raman spectroscopy. There is no need to open the bag and take a physical sample to verify the product; the closed bag can be scanned and verified upon delivery, saving multiple testing steps.

Direct Dispense Systems: Time and Cost Savings

Expanding the use of Direct Dispense systems provides a flexible manufacturing technology designed to help biopharmaceutical manufacturers maximize the efficiency and utilization of cleanroom packaging suites. There are multiple efficiencies associated with the use of these systems:

- Labor: Eliminates the time and cost of personnel who need to weigh, subdivide and dispense materials from bulk containers.
- Cross-contamination: The risk of cross contamination—by trace elements not properly removed from the cleanroom after a prior subdivision step, or contamination from cleanroom personnel failing to follow antiseptic procedures—is essentially eliminated.
- Facilities: Use of Direct Dispense systems can eliminate the need for dedicated raw material clean room preparation areas, drum storage and handling equipment, and environmental (temperature and humidity) controls for those areas.
- Testing/validating: Use of Raman testing and tailgate samples greatly simplifies the testing identification step.
- Quality: Pre-weighed Direct Dispense systems eliminate the need to clean the weighing and dispensing area for another operation, thereby saving time and reducing cross-contamination risks.
- Material stability and efficient use: Reduced-clumping packaging design improves raw material yields by avoiding material non-conformities and inaccurate ingredient measurements from severely clumped materials.

Efficient Packaging Drives Productivity

Avantor is committed to offering packaging solutions like the J.T.Baker® Direct Dispense packaging platform—innovative technology engineered to match customers' specific usage, cost and operational requirements. While Direct Dispense technology may not fully replace the cleanroom packaging suite, it does offer a method to help increase cleanroom operational efficiency and enhance biopharmaceutical process productivity and quality.

> **The United States is the largest producer of biopharmaceuticals, approaching 60% of the global market**

Changing Landscape of the North American Pharmaceutical Market and How it Impacts Big Pharma's Procurement Strategy and Those who Support It

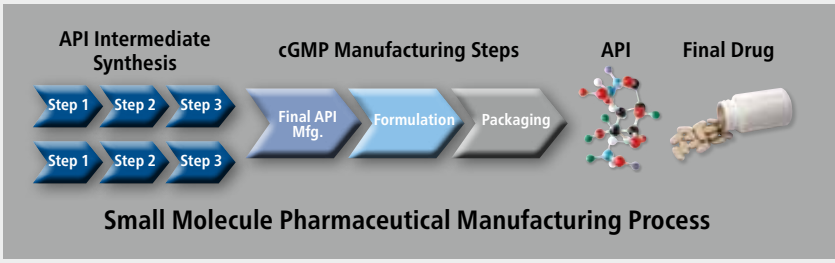
Jim Luchsinger, Biopharma Production Solutions, VWR

The North American Pharmaceutical Industry has seen a significant change over the past 10-15 years, such as the continued off-shoring of small molecule active pharmaceutical ingredients (APIs). Over the next several years, it is expected that 80% of APIs will be outsourced, with the majority coming from China and India. At the same time, the United States has become the largest producer of biopharmaceuticals, capturing in excess of 60% of the global market. Not only are the differences between a traditional small molecule API and an API grown in a biopharmaceutical process stark, but the different raw materials and quality procedures required are also very different. With the mix of pharmaceuticals produced in North America changing, the way raw material manufacturers and distributors support this industry must also continue to adapt to meet these new, and often times, very demanding needs.

The table below highlights some of the most obvious differences between a small molecule API and the much more complex large molecule biopharmaceuticals:

Large Molecule Biopharma	Small Molecule
Manufactured from living cells	Manufactured from chemical synthesis
Large/complex molecules (30,000 to 150,000 Daltons)	Small (<1,000 Daltons)
Difficulty to fully characterize final product	Final product characterized with current analytical methods
Relatively young market	Mature market
Fragile	Stable
Parenteral dosage form	Variety of dosage forms

Most notably, traditional small molecule APIs are produced from organic synthesis in highly controlled processes, while biopharmaceuticals are created by engineering a cell to produce a protein, generally grown either in mammalian cell culture or bacterial fermentation (i.e. *e. coli*). In order to grow these cells, a complex combination of high quality materials needs to be sourced and managed. These materials include the cell culture media (which can include an assortment of over 100 inorganic and organic materials manufactured from animal, plant, and other sources), inorganic salts, carbohydrates, amino acids, biological buffers such as TRIS, and a vast array of other materials. These materials are needed in order to feed and stabilize the cells during the upstream manufacturing process and to stabilize the protein during the downstream purification process. After the protein has reached the desired purity, it needs to be combined with the appropriate excipients and filled aseptically. Compared to the typical small molecule API that has no more than a dozen excipients, the additional complexity of the supply chain for biopharmaceuticals is obvious. Biopharmaceuticals are generally 100 to 200 times larger than a typical API, making them that much more difficult to characterize. Combined with the relatively fragile nature of biopharmaceuticals, this complexity increases the need for strict oversight of the supply chain in order to remove as much variability from the process as possible.



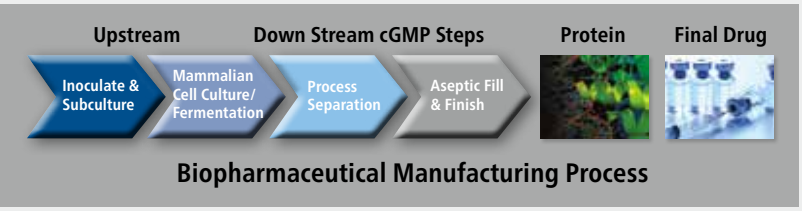
Small Molecule Pharmaceutical Manufacturing Process

Current trends in the industry compound the challenge further. The growth of biopharmaceuticals is nearly double that of the small molecule market. Recent tragedies involving diethylene-contaminated cough syrups, melamine-contaminated infant formulas, and nearly 100 deaths connected to intentionally adulterated heparin, have led to increased demand for greater transparency and tighter controls over the raw material supply chain.

Greater control and oversight of the supply chain is a noble goal, but there are significant hurdles to overcome before that goal can be met. While major components such as biochromatography resins and filters have significant transparency back to the manufacturers, many process chemicals and excipients have a much more complicated supply chain.

For many of the materials that are used in significant quantities, no original manufacturer is willing to utilize the appropriate PE bags and pails required by the industry. For other materials with no true vertically integrated cGMP manufacturer in existence, a significant portion of the supply base simply repackages materials purchased from other manufacturers. These repackaged materials may be put into solution, purified, and recrystallized under cGMP standards. In many cases, the result is a high quality product that has been packaged appropriately with the required specifications for the intended use, but this process still greatly complicates the required transparency and increases the possibility of a lapse in the supply chain.

In order to navigate the challenges of this complex supply chain, it is critical to align with providers that actively manage sources of supply. VWR offers solutions that include Change Notice Verification Services, multiple redundant storage locations, and primary and secondary sourcing options. Learn more about how VWR can help mitigate risks in your supply chain by contacting your local VWR Representative.



Biopharmaceutical Manufacturing Process

1. Bioprocessing International 11(3) 2013. Global Evolution of Biomanufacturing.

Don't Take Your Source of Biological Buffers for Granted!

Carl Schrott, Bioprocessing Technologies Manager, VWR

Biological Buffers play a critical role to ensure that the pH of the culture system mimics as best it can that of the natural environment for the cells being studied. Phosphate and bicarbonate buffers have long been used. However, both have limits. Phosphate buffers can form insoluble complexes with essential components in the nutrient media. In addition to their role in buffering the system, bicarbonate/CO_2 is involved in biochemical reactions within the culture environment.

The use of Zwitterionic Organic Buffers (ex. HEPES, PIPES) began in the 1960s[1] . Also known as Goods Buffers[2], these have proven useful in culture systems and have several favorable characteristics such as:

- pKa values with acceptable pH ranges of 6.0 to 8.0
- Chemically inert in the presence of inorganic salts thus, nonreactive with other media components
- They do not absorb wavelengths required to measure purification column performance
- Improved protein stability

In the Volume 1 2015 edition of Production Insight, VWR Bioprocessing announced a new offering of Biological Buffers and Amino Acid Derivatives. As a follow-up to this announcement, VWR is providing additional information that will assist you in the selection of biological buffers for your critical application.

- VWR's biological buffers are manufactured in the U.S. at its Sanborn, New York location. Supply chain security and transparency is much improved compared to sources from international-based companies.
- Our biological buffers are synthetically manufactured. The risk of TSE/BSE contamination associated with raw materials made with animal-derived components has been eliminated.
- VWR's Sanborn manufacturing site is ISO 9001 and ISO 13485 certified. Products are manufactured in a GMP environment and assurance is guaranteed under an audited quality system program.
- VWR's manufactured buffers have been successfully used in preclinical, clinical, and licensed biological applications. Thus, we have a proven track record of providing the highest quality buffers required for your critical bioprocessing applications.
- VWR manufactures the largest lot sizes of buffers available in the industry. This provides assurance that your supply chain needs are routinely met.

Our biological buffer offering is available ready-to-ship in 1KG, 5KG, and 25KG unit packaging. If you need larger pack sizes (ex. 50KG, 100KG), or you require these buffers in other formats (ex. Liquid), VWR Custom Manufacturing Services can assist in your custom requirements.

Footnotes:

1. J. gen Virol. (1968), 2, 309-312
2. Good, Norman E., etal, Biochemistry 5 (2) 467-477

Quality Assurance Considerations in Single-Use Manufacturing

Scott Jennings, Director, Quality & Regulatory Compliance, VWR

The use of single-use technology in biopharmaceutical manufacturing has been gaining increasing attention and adherence in recent years. The technology incorporates a wide range of polymer-based, disposable fluid-handling components (generally comprised of tubing, bags, bottles, filters, sensors, connectors and other componentry) that are pre-fabricated and installed to support applications from upstream bioprocessing to final formulation and filling. After being used once in support of a drug manufacturing process or campaign, these products are removed, disposed of and a replacement is installed.

Typically, custom single-use assemblies are designed and fabricated by single-use manufacturers in consultation with the engineering and compliance organizations of drug companies who specify that these assemblies be provided pre-sterilized - often by exposure to gamma-irradiation. This means that the single-use manufacturer bears the responsibility, not only for the implementation and use of current Good Manufacturing Practices (cGMPs) during the manufacturing process, but also for maintaining a compliant sterility validation program.

As such, there are several significant and unique quality assurance and regulatory compliance considerations faced by Quality departments of single-use manufacturers to address the inherent risks associated with the production of sterile assemblies that come into direct contact with drug substances. These considerations include, but are not limited to:

- Cleanroom certification and contamination control
- Environmental monitoring
- Sterility and sterile-barrier packaging validation

Our single-use manufacturers support biopharmaceutical companies in implementing single-use technologies that reduce contamination risk, improve resource efficiency and lower labor and energy costs. This article provides a discussion of the quality and regulatory foundations upon which our 'best in class' single-use manufacturing is based.

All VWR single-use sites are certified and adhere to the relevant ISO standards (including ISO 14644) and have implemented the best practices as appropriate.

Cleanroom Certification and Contamination Control

Since single-use products are often placed into use with no pre-cleaning or sterilization steps by the end user, the need for contamination controls during single-use manufacturing is paramount. Single-use production environments are designed and maintained to the ISO 14644 series of cleanroom standards. The ISO 14644 series addresses the standardization of equipment, facilities and operational methods for cleanrooms and other controlled environments. Specifically, ISO 14644-1 defines "classes" of cleanroom environments based on air cleanliness by particle concentration.

Compliance to a specific ISO classification is established through a defined certification process, maintained by routine monitoring (as specified in ISO 14644-2), and re-certified at least annually. Cleanroom certification, which is normally performed by third party certification specialists, involves not only the measurement and reporting of particle concentration data, but also airflow volumes, air changes per hour calculations, and room-to-room differential pressures against defined acceptance criteria.

Currently, single-use manufacturing facilities are most often classified to ISO Class 7, where particle concentrations must meet the following requirements.

ISO Class 7		
Maximum allowable concentrations for particles equal to, and greater than, the sizes shown below		
0.5 µm	1 µm	5 µm
352 000 particles/m^3	83 200 particles/m^3	2930 particles/m^3

Cleanroom contamination control, however, extends beyond the simple measurement and monitoring of particle concentrations in manufacturing areas. Industry best practices for single-use manufacturing are based on cleanroom environments that include the following elements:

- Separate, adjacent personnel gowning rooms, certified to ISO Class 8, with personnel gowning practices that are established, communicated through personnel training, and consistently followed by cleanroom technicians. For ISO Class 7, this generally includes hair covers (head and beard), frock or coverall, shoe covers or dedicated cleanroom shoes and gloves
- Separate, adjacent material transfer rooms or airlocks, certified to ISO Class 8, with material transfer practices that minimize the likelihood of introducing contaminants into cleanroom manufacturing areas that may be present on the surfaces of incoming materials or material packaging
- A detailed housekeeping program for all classified areas that includes routine cleaning of all surfaces with the rotational use of two or more germicidal cleaning agents and one or more sporicidal cleaning agents. The cleaning program should be validated to establish efficacy
- Line clearance procedures that establish practices for lot-to-lot or job-to-job material clearance and area/equipment cleaning to reduce the risk of cross-contamination or mix-ups in materials from one lot/job to the next

Environmental Monitoring

We have discussed the measurement and monitoring of non viable particles upon which cleanroom certification and classification is based. However, there are four additional aspects of environmental monitoring that are critical to environments where single-use products that support drug manufacturing are produced. These are differential pressure monitoring,

non-viable particle monitoring, temperature and humidity monitoring and viable microorganism monitoring.

Differential pressure monitoring

Maintenance of cleanliness and control of airborne contaminants in single-use cleanroom manufacturing facilities is supported by an airflow design that ensures that air always flows from: (a) classified rooms to adjacent non-classified rooms, and (b) from lower classified rooms to adjacent, higher classified rooms (e.g., from an ISO Class 7 area to an ISO Class 8 area). Ensuring that these positive differential air pressures are maintained requires continual monitoring.

Differential pressure monitoring is usually performed using magnehelic gauges. These gauges have a sensitive diaphragm that responds to changes in pressure from one point to another. Monitoring of differential pressures in a cleanroom facility can be performed either by taking periodic, manual readings of the magnehelic gauges, or by an automated monitoring system that transmits and records the readings. Readings that are found to be outside of established limits would require a CAPA investigation, correction and a risk assessment related to potential impact of contamination to the cleanroom and manufactured product.

Non-viable particle monitoring

As described previously, ISO 14644-1 "classes" of cleanroom environments are based, in part, on air cleanliness by particle concentration. The particles measured during the cleanroom certification process are referred to most often as "non-viable" particles. The requirements for claiming compliance to an ISO classification, however, extends beyond an initial verification that particle concentrations adhere to defined limits. Requirements also extend to routine monitoring to ensure that particle concentrations in defined locations within the cleanroom facility continue to adhere to those limits.

This monitoring of non-living particles is sometimes done using measuring equipment placed inside the cleanroom area tied to a software system that provides automated notification of particle counts that exceed prescribed ISO limits. Portable, handheld particle counters are also used for performing routine monitoring. The end result for the single-use manufacturer must be an ongoing program for verifying that non-viable particle counts in cleanroom locations continue to meet ISO-prescribed limits for particle concentrations.

Temperature and humidity monitoring

The need for monitoring the temperature and humidity of a single-use cleanroom manufacturing space may, at first, appear unnecessary. From the standpoint of the likelihood of an adverse effect on the physical properties of polymer-based, single-use componentry, it might seem like the temperature and humidity profiles of a manufacturing environment with an operational HVAC system would not be a factor. However, the temperature and humidity profiles of a manufacturing space can have a potentially significant impact on the growth and spread of microorganisms in the air and on the surfaces of cleanroom manufacturing areas.

For this reason, most single-use cleanroom facilities have systems that provide continuous monitoring of temperature and humidity. These systems provide calibrated sensors mounted in key locations in the manufacturing, gowning and material transfer areas that collect periodic temperature and humidity readings and transmit them to a software-based monitoring system. The monitoring system is programmed to collect the data, compare the measurements to pre-set alert and action limits, and provide automatic notifications to key personnel when alert and action limit excursions occur. Such notifications would typically result in the initiation of CAPA activity to investigate and correct the condition causing the excursion.

Because temperature and humidity monitoring is generally performed for controlling microbial growth, the setting of temperature and humidity limits is often tied to another environmental monitoring activity – that of viable microorganism monitoring.

Viable microorganism monitoring

The control of bioburden – defined as the population of viable microorganisms on a product and/or product packaging – is critical for single-use manufacturing, particularly in cases where sterility validation is a factor (see the section on sterility validation below). As a result, the routine

Custom aspectic sampling system

monitoring of living (i.e., viable) microorganisms in cleanroom areas is an essential part of a contamination control program for single-use manufacturers.

The practice of viable microorganism monitoring involves periodic collection of samples from the air, surfaces (such as walls, floors, ceilings, tables, racks) and sometimes personnel (such as gowning and gloves). Samples are collected from pre-defined locations and placed onto contact and/or settling plates containing an agar growth media. These plates are then incubated in a laboratory to promote growth and the plates are 'read' by a qualified lab technician to identify and count microbial colony-forming units (CFU's).

Results from viable microorganism monitoring are most often reported in the form of a total bacterial count and total fungal count, in CFUs. Further reporting refinements may also specify counts for moulds, yeast and other forms of microbial growth. Alert and action limits are defined for these counts, and excursions investigated and corrected through the CAPA system.

Sterility and Sterile Barrier Packaging Validation

Perhaps the greatest challenge facing the quality/regulatory departments of single-use manufacturers today is found in process validation. Specifically, unique validations that are required in support of the provision of sterile product to their biopharmaceutical customers.

In the biopharmaceutical industry today, single-use assemblies, more often than not, are provided "pre-sterilized" – that is, having undergone a terminal sterilization process such as gamma-irradiation. It is the single-use manufacturer who is responsible for subjecting the product to the sterilization process (either in-house or, more likely, outsourced to an approved sterilization facility). Regardless of where the sterilization takes place, it is always the responsibility of the single-use manufacturer to perform the validations relative to the sterilization process being conducted on its manufactured products.

Sterility validation

Sterilization is defined as a validated process used to render product free from viable microorganisms. It should be noted, however, that in a sterilization process, the nature of microbial inactivation is exponential and, thus, the survival of a microorganism on an individual item must be expressed in terms of probability. While this probability can be reduced to a very low number, it can never be reduced to zero.

This fact has led to the term Sterility Assurance Level (or SAL) which is defined as the probability of a single, viable microorganism occurring on an item after sterilization. The term SAL takes on a quantitative value, generally 10^{-6} or 10^{-3}. When applying this quantitative value to assurance of sterility, an SAL of 10^{-6} has a

lower value but provides greater assurance of sterility than an SAL of 10^{-3}. Stated simply, a Sterility Assurance Level of 10^{-6} means that there is literally a million-to-one chance that a manufactured product will contain a living microorganism, post-sterilization.

In today's single-use industry, where sterile products are being provided to the drug manufacturing end-user, an SAL of 10^{-6} is most often required. To attain an SAL of 10^{-6} through the use of gamma-irradiation, the single-use manufacturer is required to develop and successfully execute a validation protocol based on the validation methodology defined in ANSI/AAMI/ISO 11137-1:2006, *Sterilization of healthcare products - Radiation - Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices* and ANSI/AAMI/ISO 11137-2:2006, *Sterilization of healthcare products - Radiation - Part 2: Establishing the sterilization dose*.

For organizations (such as those that comprise of VWR Single-Use Solutions manufacturing sites) who manufacture custom, integrated, gamma-irradiated products to drug manufacturing customers, the ANSI/AAMI/ISO 11137 Standards specify the use of a simulated product. The simulated product is a worst-case test sample that is specifically designed and fabricated for the establishment and maintenance of the sterilization dose. VWR Single-Use Solution sites each have a defined, simulated product that represents their product family of gamma-irradiated assemblies, based on the following criteria specified in ANSI/AAMI/ISO 11137.

- The simulated product is similar to the actual suite of products in terms of materials and size, and is subjected to manufacturing processes in use at the site
- The simulated product constitutes an equivalent or greater challenge to the sterilization process than that provided by individual components of the product family

This simulated product is subjected to bioburden and sterility testing in accordance with ANSI/AAMI/ISO 11137-2 in order to provide initial validation of radiation sterilization of a healthcare product, and the radiation sterilization process is re-validated through quarterly dose audits. Execution of this validation ensures the maintenance of a SAL of 10^{-6} for the site's product family when subjected to a gamma irradiation dose of at least 25 kGy.

Choice
- Open architecture
- Strong supplier management program
- Vertical integration
- Speciality fittings
- Stoppers and bags

Expertise
- Extensive fluid handling connectivity knowledge
  - Single-use facilities
  - Hybrid facilities
  - Conversion from self-assembled parts

Service
- Local single-use experts
- Expedited design and approval process
  - Designs <3 days
  - Validation packs <3 days

Sterility barrier packaging validation

The single-use manufacturer is responsible for validating initial sterility through methodologies defined in ANSI/ AAMI/ ISO 11137, described above. But the following question naturally arises for end users who are receiving sterile product from single-use manufacturers: "How long does the delivered product remain sterile when stored in its original packaging in accordance with stated storage conditions?" To answer this question, the single-use manufacturer must use another validation standard, specifically ANSI/AAMI/ISO 11607 - Packaging for Terminally Sterilized Medical Devices.

- Part 1: Sterile barrier systems and packaging system
- Part 2: Validation requirements for forming, sealing and assembly processes

Many single-use assemblies are packaged using a double layer of non-porous, polyethylene bag material where both the inner and outer bags are heat-sealed. The drug manufacturer will typically remove the outer bag prior to bringing the product into the manufacturing suite, thus leaving the product within the inner bag, which (in most cases) represents the "sterile barrier" for the product. In other words, if the sterile barrier (i.e., inner bag) is intact, the product within may be considered as remaining sterile.

The sterile barrier packaging validation methodology, as specified in ANSI/AAMI/ ISO 11607, supports the single-use manufacturers need to define a sterile shelf life for its gamma-irradiated products. The single-use manufacturer packages a specified number of test samples of its products (or, test samples designed to simulate a worst-case profile for its packaged products), subjects the samples to gamma irradiation at the high end of its dose range, and subjects the samples to a series of laboratory tests to validate a sterile shelf life. These tests include:

- Accelerated aging – to simulate the degradation of packaging over time (corresponding to the desired shelf life duration) at specified storage conditions
- Dye penetration – to establish the leak integrity of heat seals after aging
- Seal-peel testing – to identify seal-strength degradation of heat seals after aging
- Sterility testing – to demonstrate the sterility of the contents of packaged products after aging

With successful results, the single-use manufacturer can make a sterile shelf life claim for products packed in accordance with its validation protocol, and gamma-irradiated at an approved irradiation facility to the specified dose range.

Conclusion

The single-use manufacturer today is faced with unique challenges in fulfilling the expectations of its biopharmaceutical customers and the regulators who are applying ever-expanding controls over this emerging industry. Many of these challenges directly impact quality and regulatory compliance organizations within the single-use manufacturing organization. It is only by carefully applying the standards and methods discussed here that these manufacturers can establish a foundation for continuing to provide the industry with safe and effective single-use solutions.

Bulk Drug Substance Collection System

For more information on these products, contact your local VWR sales Representative, or visit **vwr.com/single-use**

The Importance of Endotoxin Control in Process Consumables

By Kathy Miscioscio and Karen Rossington, Contec, Inc.

To ensure the quality of the medicines they produce, pharmaceutical, biopharmaceutical and medical device manufacturers must carefully choose the process and cleaning consumables used to clean and disinfect the production suites. In addition to choosing products that are suitable for the task at hand, whether picking up spills, applying disinfectant, or wiping surfaces, it is also important that these consumables do not contribute particle and microbial load to the environment. Typical parameters of concern when choosing process consumables are fiber and particle levels, sorbency, non-volatile residue and ionic contamination. For aseptic manufacturers, the level of sterility assurance is also important. For critical applications in these environments, the level of endotoxins in process consumables should also be considered.

What are Endotoxins

The presence of pyrogens is a critical safety concern since these substances cannot be easily removed.

Products contaminated with pyrogens can pose a life-threatening risk to patients. Unlike viable microbial contaminants which can be destroyed by various sterilization techniques, pyrogens are difficult to remove and deactivate. Bacterial endotoxins, specifically from the outer membranes of gram-negative bacteria, are the most common pyrogens so much so that term is often used interchangeably.

"Microbial pyrogen" as opposed to "gram negative bacterial endotoxin" has become a general descriptive term for many different substances. However, pyrogenic substances can be produced by some gram positive bacteria, mycobacteria, fungi and also viruses, but the pyrogens produced by gram negative bacteria, i.e., the endotoxins, are of significance to the pharmaceutical industry. These bacterial endotoxins, found in the outer membrane of gram-negative bacteria, are members of a class of phospholipids called lipopolysaccharides (LPS). LPS are not exogenous products of gram negative bacteria. The release of LPS from bacteria takes place after death and lysis of the cell. Good examples of pyrogen producing gram- negative bacteria are *Escherichia coli*, *Proteus, Pseudomonas, Enterobacter and Klebsiella*."[1]

Endotoxin Limits

The FDA sets the limits for pharmaceutical products produced in the US or imported into the US. Endotoxin is expressed in International Units (IU) of endotoxin although Endotoxin Unit (EU) is still commonly used. One International Unit of endotoxin is equal to one Endotoxin Unit.

The limits for endotoxins are stated in the USP chapter< 161>, Transfusion and Infusion Assemblies and Similar Medical Devices. The USP requirement for medical devices specifies a limit of 0.5 EU/mL or 20 EU/device for products that directly or indirectly contact the cardiovascular and lymphatic systems. The limit for products in contact with the Cerebrospinal fluid is 0.06 EU/mL or 2.14 EU/device.[2]

Sources of Endotoxins

The US FDA states that "It is difficult to remove endotoxins from products once present. It is far better to keep finished products and components relatively endotoxin-free rather than have to remove it once present."[1] Therefore, it is important to control the level of endotoxin units in materials used in the production of drug products and medical devices.

Endotoxins can be introduced into a product or process by operators, raw materials, packaging materials, solvents (such as cleaning products), etc. that are used in the formulation or manufacture of pharmaceuticals. Water used as a solvent or in the processing of the product can also be a source of endotoxins.

Preventing Endotoxin Contamination

Water for Injection (WFI) is used in the production of parenteral drugs and other critical products when endotoxin levels must be controlled. The limits for bacterial endotoxins

in WFI are ≤ 0.25 EU/mL or ≤0.25 I.U./mL as stated in the USP Monograph on Water for Injection[3] and the European Pharmacopoeia, Water for Injection Monograph[4], respectively.

There are no regulations for endotoxin levels in cleanroom wipes and alcohol products, however, convention is that low endotoxin products meet the USP requirement of <0.5 EU/mL or <20 EU/device. Products certified as low endotoxin are not required to use low endotoxin ingredients, but the final product must be tested for conformance to USP requirements for endotoxin levels. Finished products containing WFI have a component (water) that is low endotoxin, but for the finished product to be classified as low endotoxin, it must be tested to meet the stated limits to ensure all components of the product, packaging and manufacturing cycle have been controlled to produce a low endotoxin result.

Summary

It is much more effective to prevent the introduction of endotoxins into processes and products than it is to remove them downstream. It is important to control the microbiological levels of products and processes, monitor the water used in production, and control the endotoxin levels of incoming raw materials to prevent the formation and introduction of endotoxins. The use of low endotoxin products for cleaning can also minimize the risk of endotoxin contamination of a pharmaceutical product. Contec makes a full line of low endotoxin certified products, including presaturated wipes, dry knit and nonwoven wipes, and sterile 70% isopropyl alcohol, for the most critical applications. Each lot is tested before release to ensure a low level of endotoxin.

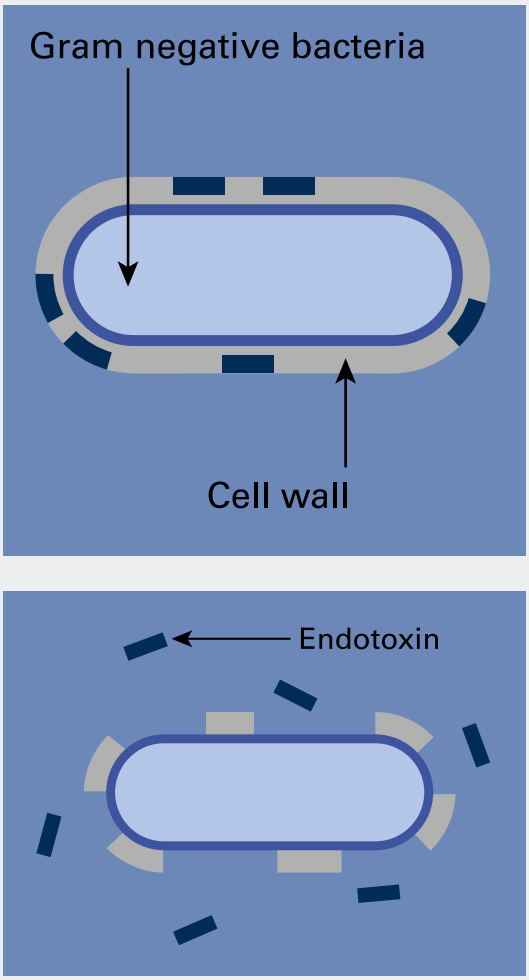
References

[1] FDA Inspection Technical Guides > Bacterial Endotoxins/Pyrogens, Date: 3/20/85 Number: 40

[2] USP chapter < 161>, Transfusion and Infusion Assemblies and Similar Medical Devices

[3] USP Monograph, Water for Injection

[4] European Pharmacopoeia, Water for Injection Monograph (0169)



Cleanroom Cleaning Protection

By Jennifer Galvin, Ph.D. and Mark Tartaglia, CIH, MSPH, DuPont

Cleaning and disinfection protocols are an important aspect of cleanroom operations, to meet environmental monitoring requirements, to meet any regulatory requirements and to minimize the risk of contamination. Cleaning and disinfection are especially important in cleanrooms for aseptic processing, healthcare applications, compounding pharmacies, lab animal research facilities and others.

There are many terms to describe the formulations used for cleaning and control or elimination of viable organisms, each with a different composition and intended use. Depending on the need, cleaning might involve a detergent, sterilant, sporicide, or other disinfectant. Choice of cleaning and antimicrobial agents involves consideration of many factors, including regulatory requirements, material compatibility, application method, amount and type of organisms to be killed or controlled, amount and type of soil to be removed, and others. In addition to selecting which agents to use a cleaning protocol must also be outlined.

Cleaning protocols often include routine use of disinfectants with periodic use of sporicides to maintain environmental control. Frequency of rotation between these agents can depend on many factors specific to a given facility: as set by schedule, as indicated by environmental monitoring, or as part of facility recovery after disruption of normal operations, such as after construction. A key part of the protocol is protecting the environment and employees who are performing the tasks the protocol requires.

How do I protect my employees and my process?

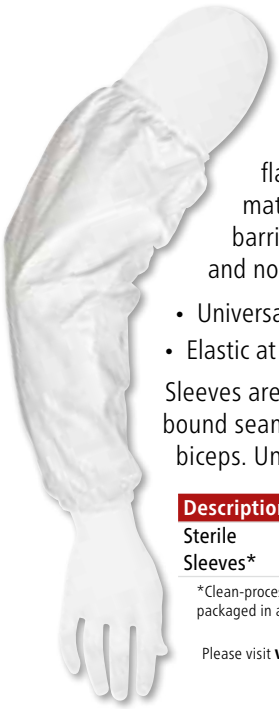
Employee protection is a necessary consideration for any cleaning protocol. Hazards can include skin or eye contact, respiratory exposure, and even slips, trips and falls. For cleanroom use, properties such as garment cleanliness, particle shedding, filtration efficiency, etc., should be part of your personal protective equipment (PPE) garment evaluation criteria. In aseptic cleanroom environments, sterile garments and accessories may be required.

Given the breadth of hazards, no single garment solution is appropriate for all cleaning applications, so it's important to conduct a hazard assessment to understand all potential scenarios and protect employees effectively. In addition to a broad selection of protective garments, DuPont Protection Solutions has a Certified Industrial Hygienist available who can assist customers with these complex decisions.

Cleaning a Biological Safety Cabinet:

Biological safety cabinets (BSC) are a common engineering control device found in many life science, biotech and pharmaceutical work environments. These devices, as well as other pieces of equipment that handle biological hazards, need to be cleaned on a regular basis. The level of antimicrobial cleaning agent used depends on a number of factors, including the microorganism(s) being handled and the degree of cross-contamination prevention or microbial reduction required.

Routine daily cleaning to prevent cross-contamination between tasks in the BSC may involve wiping down the interior surfaces with 70% isopropanol. If a higher level of cleaning is needed to satisfy end-of day or weekly cleaning regimens, phenolic or even sporicidal cleaners may be applied using wet-wiping or spray application techniques. Standard PPE for this type of cleaning includes a lab coat, sterile sleeves, nitrile or latex exam gloves and safety glasses.



DuPont™ Tyvek® IsoClean® Sleeves

Sleeves are constructed of Tyvek® flashspun polyolefin protective material that provides an effective barrier to dry particles, microorganisms, and nonhazardous liquids.

- Universal size
- Elastic at both ends

Sleeves are 45.7 cm (18") long and feature bound seams, and covered elastic wrists and biceps. Universal size. White.

Description	Packaging	Cat. No.
Sterile Sleeves*	Individually Packaged	**89125-646**

*Clean-processed – processed to minimize particle shedding and individually packaged in an ISO Class 4 (FED-STD-209E Class 10/M2.5) cleanroom.

Please visit **vwr.com/dupontprotection** for more options.

DuPont™ Tyvek® IsoClean® Hoods with Full Face Opening

Hoods are constructed of Tyvek® flashspun polyolefin protective material that provides an effective barrier to dry particles, microorganisms, and nonhazardous liquids.

- Flashspun polyolefin
- Bound seams, ties with loops for fit
- Universal sizing

Hoods feature bound seams, full face opening, bound hood opening, and ties with loops for fit.

Size	Packaging	Cat. No.
Universal (Non-Sterile)	Bulk	**89125-648**

Please visit **vwr.com/dupontprotection** to view a full listing of offerings.

DuPont™ Tyvek® IsoClean® Lab Coats

Lab Coats provide protection and durability while remaining comfortable.

- Coats provide an outstanding barrier against dry particles, nonhazardous liquids, and microorganisms
- Designed for use in cleanroom environments where protection is critical
- Limited-use lab coats are antistatic-treated, low-linting, and chemically and biologically inert

Lab coats feature serged seams, laydown collar, five-snap front, one breast pocket, two hip pockets, and open wrists. All coats feature Raglan sleeves.

Size	Cat. No.
S	**89127-196**
M	**89125-612**
L	**89127-194**
XL	**89125-614**
XXL	**89127-190**

DuPont™ Tyvek® IsoClean® Frocks with High Mandarin Collar and Set Sleeves

Frocks are constructed of Tyvek® flash-spun polyolefin protective material that provides an effective barrier to dry particles, microorganisms, and nonhazardous liquids.

- Effective barrier to dry particles, microorganisms, and nonhazardous liquids
- Front snap closure
- Serged seams, elastic wrists, and 6 snap closures

Frocks feature serged seams, high mandarin collar with snap, set sleeves, elastic wrists, and six snap closures.

Size	Cat. No.
S	**89127-304**
M	**89125-620**
L	**89127-302**
XL	**89125-622**
XXL	**89127-296**

Please visit **vwr.com/dupontprotection** to view additional sizes.

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Kimtech* is asking pharmaceutical manufacturing production managers to take a closer look at their existing reusable apparel. Is it protecting their process and their people? Or is it a potential cause of contamination?

Since people are the largest source of contamination, if their garments are compromised a manufacturer's process could be too. Selecting the right garment can dramatically reduce this risk. Kimtech Brand* single-use apparel can control this threat by simplifying the contamination control process. How? Contact your VWR representative to find out what it means to be ***Dressed For Success***.

Sterile Coveralls

Size	Cat. No.
Small	89092-898
Medium	89092-900
Large	89092-902
X-Large	89092-904
XX-Large	89092-906
3X-Large	89092-908
4X-Large	89092-910
5X-Large	89166-188
6X-Large	89166-190

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There are important differences in cleanroom glove manufacturing and technology that can impact the way a glove feels and performs. We believe that the glove mold used makes all the difference in the fit and feel of the glove.

The Cardinal Health™ Glove mold features an independent thumb design — meaning the finger placement replicates the anatomical position of a resting hand — allowing for natural, comfortable movement.

One study shows that gloves featuring an independent thumb require less force for similar displacements of the thumb than those gloves produced without an independent thumb feature.[1]

No matter what type of cleanroom you are in, gloves produced on a mold with an independent thumb design ultimately can help reduce hand fatigue so you can perform at your best.

Visit **vwr.com/cardinalgloves** to view our full portfolio.

[1] Bennet, M. A. & Tekamp, D. A. Surgical Glove Comparison Testing. Stress Engineering Services. February 2012.

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- First Line Barrier
- Color Coding

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VWR® Industrial Lab Coats
VWR® Industrial Bouffant Caps
VWR® Industrial Nylon Hairnets
VWR® Industrial CPE Shoe Covers
VWR® Industrial Beard Covers
VWR® Industrial Aprons

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Lab Coats

Bouffant Caps

Nylon Hairnets

Shoe Covers

Beard Covers

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Providing exceptional grip, sensitivity and cytotoxic protection, BioClean Ultimate™ Sterile Polychloroprene Gloves have excellent antistatic properties and offer both chemical protection and outstanding tactility. Part of the BioClean-C™ Chemotherapy range, the Ultimate is latex-free and powder-free.

- Textured for improved grip
- Powder-free & latex-free
- Antistatic properties
- Beaded cuff for strength
- Excellent chemical resistance
- Double-donnable
- Non-particulating EasyTear™ packaging
- Color: Natural
- Length: 30.5 cm (12")
- Thickness: Cuff: 3.54 mil, Palm: 4.33 mil, Finger Tip: 5.51 mil

Size	Cat. No.
6.0	75839-016
6.5	75839-018
7.0	75839-020
7.5	75839-028
8.0	75839-030
8.5	75839-032
9.0	75838-988
10.0	75839-014

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NEWLY EXPANDED LINE

Description	CAS No.	Formula	Molecular Weight	Grade	Available Sizes	Cat. No.
Amino Acid Derivatives						
Asparagine, Anhydrous	70-47-3	$C_4H_8N_2O_3$	132.12	Bioreagent	100g, 1kg, 5kg, 25kg	**VWRB15005**
L-Cystine Dihydrochloride	30925-07-6	$C_6H_{12}N_2O_4S_2 \bullet 2HCl$	313.23	Bioreagent	100g, 1kg, 5kg, 25kg	**VWRB21502**
Hypoxanthine Disodium Salt	102-32-9	$C_5H_2N_4O \bullet 2Na$	180.11	Bioreagent	100g, 1kg, 5kg, 25kg	**VWRB31608**
Hypoxanthine Sodium Salt	45738-97-4	$C_5H_3N_4O \bullet Na$	158.11	Bioreagent	100g, 1kg, 5kg, 25kg	**VWRB31752**
L-Lysine Anhydrous	56-87-1	$C_6H_{14}N_2O_2$	146.19	Bioreagent	100g, 1kg, 5kg, 25kg	**VWRB42307**
L-Tyrosine Disodium, Dihydrate	122666-87-9	$C_9H_9NO_3Na_2 \bullet 2H_2O$	261.19	Bioreagent	1kg, 5kg, 25kg	**VWRB87058**
Biological Buffers						
HEPES Free Acid	7365-45-9	$C_8H_{18}N_2O_4S$	238.3	Bioreagent	1kg, 5kg, 25kg	**VWRB30487**
HEPES Sodium Salt	75277-39-3	$C_8H_{17}N_2O_4SNa$	260.3	Bioreagent	1kg, 5kg, 25kg	**VWRB30567**
PIPES Free Acid	5625-37-6	$C_8H_{18}N_2O_6S_2$	302.37	Bioreagent	1kg, 5kg, 25kg	**VWRB73007**
PIPES Disodium Salt	76836-02-7	$C_8H_{16}N_2O_6S_2Na_2$	346.33	Bioreagent	1kg, 5kg, 25kg	**VWRB73305**
PIPES Sequisodium Salt	100037-69-2	$C_{16}H_{33}N_4O_{12}S_4 \bullet 3Na$	670.69	Bioreagent	1kg, 5kg, 25kg	**VWRB73257**
TRIS Hydrochloride	1185-53-1	$C_4H_{11}NO_3HCl$	157.6	Bioreagent	1kg, 5kg, 25kg	**VWRB85827**
Tromethamine (TRIS)	77-86-1	$C_4H_{11}NO_3$	121.14	USP, EP, BP, JPC, Endotoxin Tested	500g, 2.5kg, 12kg, 50kg	**VWRB497**
Carbohydrates						
Dextrose, Anhydrous	50-99-7	$C_6H_{12}O_6$	180.16	USP, EP, BP, JP, Endotoxin Tested	1kg, 2.5kg, 12kg, 100lb, 200lb	**VWRBK876**
Chaotic Agents						
Urea	57-13-6	CH_4N_2O	60.06	USP, EP, BP, JP, Endotoxin Tested	500g*, 12kg, 50kg	**VWRB568**
Inorganic Salts						
Ammonium Sulfate	7783-20-2	$H_8N_2O_4S$	132.14	ACS, NF, Endotoxin Tested	500g, 2.5kg, 12kg, 100kg	**VWRB191**
Calcium Chloride, Dihydrate	10035-04-8	$CaCl_2 \bullet 2H_2O$	147.02	USP, EP, BP, JP, Endotoxin Tested	1kg, 12kg	**VWRB556**
Potassium Phosphate Monobasic, Anhydrous	7778-77-0	KH_2PO_4	136.09	NF, EP, BP, Endotoxin Tested	1kg, 12kg	**VWRB0781**
Sodium Chloride	7647-14-5	NaCl	58.44	USP, EP, BP, JP, Endotoxin Tested	1kg, 2.5kg, 12kg, 50kg, 350lb	**VWRB241**
Sodium Phosphate Dibasic, Anhydrous	7558-79-4	Na_2HPO_4	141.96	USP, EP, Endotoxin Tested	1kg, 12kg	**VWRB0404**
Sodium Phosphate Dibasic, Heptahydrate	7782-85-6	$Na_2HPO_4 \bullet 7H_2O$	268.07	ACS, USP, Endotoxin Tested	1kg, 12kg	**VWRB0348**
Sodium Phosphate Monobasic, Monohydrate	10049-21-5	$Na_2HPO_4 \bullet H_2O$	137.99	ACS, USP, BP, Endotoxin Tested	1kg, 12kg	**VWRB0823**
Sodium Sulfate, Anhydrous	7757-82-6	Na_2SO_4	142.04	USP, EP, Endotoxin Tested	500g, 2.5kg, 12kg, 100kg	**VWRB836**

*This specific product is not available in Canada. Please contact your VWR Sales Representative to learn about easy access to similar options available in your region.

For complete listing, go to **vwr.com/bioprocesschemicals**

For more than a century, the J.T.Baker® brand has stood for excellence along every step of our customers' processes—from the laboratory to full-scale production.

J.T.Baker® High-Purity Acids

Offered in four distinct levels of purity for general use to trace-metal analysis

Description	Size	Packaging	Cat. No.
Acetic Acid, Glacial, BAKER ANALYZED® A.C.S. Reagent, (Aldehyde Free)	4 L	Poly Bottle	**JT9508-6**
Hydrochloric Acid, ULTREX® II Ultrapure Reagent	500 mL	Fluoropolymer Bottle	**JT6900-5**
Hydrochloric Acid, 36.5-38.0%, BAKER INSTRA-ANALYZED® Reagent	2.5 L	Clear PVC Coated Glass Bottle	**JT9530-33**
Hydrofluoric Acid, 48.0-51.0%, BAKER ANALYZED® A.C.S. Reagent	4 L	Poly Bottle, Bagged	**JT9560-6**
Nitric Acid, 69.0-70.0%, BAKER INSTRA-ANALYZED® Reagent	2.5 L	Clear PVC Coated Glass Bottle	**JT9598-5**
Nitric Acid, ULTREX® II Ultrapure Reagent	500 mL	Fluoropolymer Bottle	**JT6901-5**
Phosphoric Acid, BAKER ANALYZED® A.C.S. Reagent, (Orthophosphoric Acid)	2.5 L	Clear Glass Bottle	**JT0260-5**
Perchloric Acid, 70%, BAKER INSTRA-ANALYZED® Plus, for Trace Metal Analysis	500 mL	HDPE Bottle	**JT9359-1**
Sulfuric Acid, BAKER ANALYZED® A.C.S. Reagent	2.5 L	Clear PVC Coated Glass Bottle	**JT9681-33**
Sulfuric Acid, BAKER INSTRA-ANALYZED® Reagent, Low Selenium, for Trace Metal Analysis	2.5 L	Clear PVC Coated Glass Bottle	**JT9673-33**

J.T.Baker® LC/MS Solvents

High-purity to provide the performance needed with minimal risk of contaminants

Description	Size	Packaging	Cat. No.
Acetonitrile, BAKER ANALYZED® LC/MS	4 L	Narrow Mouth Amber Glass Bottle	**JT9829-3**
Acetonitrile, BAKER ANALYZED® ULTRA LC/MS	1 L	Narrow Mouth Flint Bottle	**JT9853-2**
Methanol, BAKER ANALYZED® LC/MS	4 L	Narrow Mouth Amber Glass Bottle	**JT9830-3**
Methanol, BAKER ANALYZED® ULTRA LC/MS	1 L	Narrow Mouth Flint Bottle	**JT9863-2**
Water, BAKER ANALYZED® LC/MS	4 L	Narrow Mouth Amber Glass Bottle	**JT9831-3**
Water, BAKER ANALYZED® ULTRA LC/MS	1 L	Narrow Mouth Flint Bottle	**JT9823-2**
Acetonitrile-0.1% Trifluoroacetic Acid LC/MS	4 L	Narrow Mouth Amber Glass Bottle	**JT9835-3**
Water-0.1% Trifluoroacetic Acid, LC/MS	4 L	Narrow Mouth Amber Glass Bottle	**JT9836-3**
Acetonitrile-0.1% Formic Acid LC/MS	4 L	Narrow Mouth Amber Glass Bottle	**JT9832-3**
Water-0.1% Formic Acid LC/MS	4 L	Narrow Mouth Amber Glass Bottle	**JT9834-3**

J.T.Baker® Chromatography Products

High-performance solid phase extraction columns, media and other equipment

Description	Cat. No.
BAKERBOND® Wide-Pore WP Octyl (C8) Column, Analytical	**JT7105-1**
BAKERBOND® Narrow-Pore Prep Packings	**JT7025-1**
Baker-flex® Precoated Flexible TLC Sheets, 200µm Thickness, F254, 25 x 75mm Plate, Silica Gel Coating	**JT4463-2**
Baker-flex® Precoated Flexible TLC Sheets, 250µm Thickness, F254, 25 x 75mm Plate, Silica Gel Coating	**JT4449-2**
BAKERBOND® SPE Columns, Reversed Phase, Octadecyl, 6 mL	**JT7020-6**
Extraction Disks, 50 mm	
Normal Water Samples	**JT8055-6**
Water-Samples, Polar to Non-Polar Analytes	**JT8055-7**
Diquat/Paraquat Samples	**JT8057-6**
Hydrocarbons/Oil & Grease	**JT8060-6**

VWR COLLECTION designed for every day use

VWR® Pop Up Razor Blade Dispenser

The VWR Pop Up Razor Blade Dispenser offers easy dispensing with safe blade storage.

- Reduce injuries - easy to load and remove cartridge
- Flip-open front; in-use blade holder
- Heavy-duty design with nonskid, heavy bottom
- Reloadable

Refill Cartridges are packaged 10 cartridges per case. Each cartridge is labeled with a blade type detail ("CS" for carbon steel blades, "SB" for steel back blades, "W" for washed blades, or "3" for 3 facet blades). The clamshell packaging is cleanroom ready.

VWR Pop Up Blade Dispenser Refill Cartridges

Description	Cat. No.
Pop Up Razor Blade Dispenser	**10835-969**

Blade Steel	Blade Size, in.	Coated Blade	Backing Material	Washed, Degreased	Cat. No.
2 Facet Blades					
Carbon	.009	No	Steel	Yes	**10835-967**
Carbon	.009	No	Steel	No	**10835-981**
Carbon	.012	No	Steel	Yes	**10835-965**
3 Facet Blades					
Stainless	.009	Yes	Steel	No	**10835-971**
Carbon	.009	No	Steel	Yes	**10835-973**
Stainless	.009	Yes	Steel	Yes	**10835-963**
Carbon	.009	No	Steel	No	**10835-975**
Stainless	.009	No	Steel	Yes	**10835-977**
Stainless	.009	No	Stainless	Yes	**10835-979**

CONTEC®

Contec® HydroKlean Solution

Contec HydroKlean Solution is a sterile-filled blend of 6% hydrogen peroxide and water for injection in a 34 oz (1L) bag in bottle with installed trigger sprayer. HydroKlean is ready to use, leaves little to no residue, and generates no Volatile Organic Compounds (VOC's).

HydroKlean is sterile-filled under Grade A airflow and bagged in a Grade B/ISO 5 Cleanroom. It has a certified endotoxin level of <0.25 EU/ml making it ideal for use in product contact areas. The "bag in bottle" system protects contents during use. Hydrogen peroxide is not classed as corrosive and can be used safely in all areas of a cleanroom.

Contec HydroKlean is triple bagged allowing for ease of entry into controlled environments. The linear tear bags are easy to open even when wearing gloves. Additional sizes will be available soon!

Description	Size	Cat. No.
HydroKlean Solution, Sterile Filled, with Trigger Spray	1 L (34 oz.)	**75982-112**

Perfex TruCLEAN® Mopping Systems

TruCLEAN Mopping Systems work to capture and isolate contaminants, ensuring the delivery of unadulterated cleaning and sanitizing agents. TruCLEAN Disinfection systems are designed for fast, easy application of sterilants to floors, walls and ceilings. TruCLEAN components are constructed with high-grade stainless steel, entirely autoclavable, easy to maintain and guaranteed to deliver reliable cleaning results time after time.

- Compatible with gamma, ETO and autoclave sterilization
- Reduce the risk of cross-contamination
- Multiple color combinations available

Color	Cat. No.
TruCLEAN Triple Bucket Mopping System*	
Red	**22940-012**
White	**22940-015**
Blue	**22940-014**
TruCLEAN II	
Red	**89095-990**
Blue	**89095-992**

*Also available in green and yellow

TruCLEAN® Mops and Accessories

Designed for cleanrooms or sterile environments where contamination control is extremely critical. Low profile, stainless steel mop frame compatible with all TruCLEAN mops. Easily change mop heads with our quick squeeze release and frame-locking mechanism. Choose between our polymer adjustable handle and fixed length stainless steel handle. All TruCLEAN mops can be repeatedly laundered providing exceptional value.

- Excellent chemical and microbial resistance
- Low particle generation, excellent surface coherence
- Ideal for disinfection and sterilization procedures

Description	Cat. No.
TruCLEAN Clean Room Mop	**89096-038**
TruCLEAN Microfiber Mop	**89096-040**
TruCLEAN Anti-Microbial Mop	**89096-036**
TruCLEAN Sponge Mop	**22940-023**
TruCLEAN Mop Cover	**22940-191**

10828-388
Glove Dispensers

10703-476
Safety Goggle
Dispensers

98106-922
Glove Dispensers

Dispensers for Controlled Environments

For Use in Cleanrooms, Laboratories, and Safety Applications

Organize and maintain your personal protection equipment and cleanroom supplies

- Designed to protect the cleanroom supplies from contamination
- Provide "ease-of-access" for the cleanroom workers
- Maximize space utilization for supplies in the production gowning room
- Available with wall mount brackets
- Multiple sizes and variations to cover every need
- All dispensers are also available in chemical resistant PETG material

To see our full line of products, visit **vwr.com** and enter 'S-Curve Technologies' in the search bar.

Secure & Protect

Metro® Security Storage

Protect valuable materials and sensitive items from loss or pilferage

- Security Units are available in multiple sizes and finishes, in both stationary and mobile options.
- For use any where in your facility where security is needed — Lab, Clean Room, Cooler and Stock Room
- Heavy-gauge open wire construction keeps contents visible at all times, and facilitates air flow
- Add optional Intermediate Shelves to base models, allowing flexibility to meet changing needs. Can be positioned in 1" (25mm) increments along the entire height of post.
- Double Doors open 270° and can be secured along the sides of the unit.
- Shipped knocked-down saves freight costs. Easy assembly.

1. Select the Finish
2. Choose Stationary or Mobile
3. Add Intermediate Shelves

Dry Environments		Wet Environments					
Super Erecta® Chrome Finish	Cat. No.	Super Erecta Metroseal 3™ Finish Corrosion Resistant	Cat. No.	MetroMax Q® Polymer & Epoxy Coated Steel Finish Corrosion Resistant	Cat. No.	Super Erecta Type 304 Stainless Steel Finish Corrosion Proof	Cat. No.
	82023-456		**82023-460**		**22233-690**		**82023-464**
	82023-472		**82023-476**		**22233-692**		**82023-480**
	82023-422		**82023-428**		**22233-694**		**89369-978**
	82023-424		**82023-430**				**89369-982**
	82023-426		**82023-432**				**89369-988**

For more styles and information, please visit **vwr.com**

Sklar Instruments - Buy One Get One Free!*

Sterile Disposable Instruments

- Ready to use disposable floor grade instruments offer the greatest utility at the lowest cost
- Eliminates costly cleaning, processing, and sterilization costs

Description (Case of 25)	Cat. No.
Knowles Band Scissors, 5.5"	89023-748
Metzenbaum Scissors, Curved, 7"	89023-996
Straightabis Scissors, Curved, 4.5"	89023-832
OR Scissors, Straight, S/B, 5.5"	89023-792
Mayo Scissors, Straight, 5.5"	89023-812
IRIS Scissors, Straight, 4.5"	89023-766
IRIS Scissors, Curved, 4.5"	89023-770
Halsted Forceps, Curved, 5"	89023-824
IRIS Forceps, 1/2 Curved, Serr, 4"	89023-780
Fine-Point Splinter Forceps, 4.5"	89023-756

Sterile Disposable Biopsy Punches

- Seamless cutting edge for the perfect tissue sample
- Carefully honed for a smooth razor sharp incision

Diameter (mm, Box of 25)	Cat. No.
1	10185-238
1.5	10185-260
2	10193-796
2.5	10185-236
3	10193-846
3.5	10185-264
4	10193-710
5	10192-404
6	10192-382
8	10192-424

Sterile Blades and Scalpels

- Available in a wide range of sizes and options
- SklarSafe™ Disposable Scalpels offer the unique "click and lock" shield system

Surgical Blades No. (Box of 100)	Cat. No.
Stainless Steel	
#10	82029-834
#11	82029-836
#15	82029-840
Carbon Steel	
#10	82029-818
#11	82029-820
#15	82029-824

Scalpels No. (Box of 10)	Cat. No.
#10	82029-850
#11	82029-852
#15	82029-856
SklarSafe Safety Scalpels	
#10	89025-966
#11	89025-968
#15	89025-970

*When you purchase any of these Sklar products, you will receive one free (of equal or lesser value). Visit **vwr.com/promotions** and enter **5200** to redeem!

VWR COLLECTION designed for production

VWR® Pocket Mop Cleanroom Mops

The Pocket Mop is a flat head mop that can be used for controlled environments, and is economical enough to compete with commercial mops that are often used in support or non-classified areas.

- Suited to pharmaceutical production, compounding pharmacies, food processing, nutraceuticals, hospitals and medical device
- Cleanroom grade materials of construction
- Lightweight, ergonomic hardware
- Angled head for easy application of disinfectant or detergent
- Available in NovaPoly, PolySorb, Microfiber and MegaTex materials
- Launderable/Autoclavable mop heads
- Available Irradiated

PocketMops are economical enough for single use but can be laundered and reused. Compatible with alcohol, strong disinfectants and steam sterilization.

Used with the QPSL-14 or QPSL-18 adapter, the mop is lightweight and easy to maneuver. The swivel joint rotates 360° but can be locked in a 180° movement for more precise, controlled cleaning.

Available in two standard sizes, 14" and 18", the PocketMop is available in a number of different fabrics.

PolySorb: A textured polyester – available with or without urethane foam interior

MegaTex: A non-woven, textured polyester blend with abrasive properties

NovaPoly: 100% Polyester – with urethane interior or microfiber interior

Microfiber: For dry and wet mopping and for glass and high-gloss surfaces. Available with or without urethane foam interior.

Description	Cat. No.
14" PolySorb	10029-718
14" PolySorb IR	10029-720
14" PolySorb, No Foam	10029-722
18" PolySorb	10029-724
18" PolySorb IR	10029-726
18" PolySorb, No Foam	10029-728
14" MegaTex	10029-730
14" MegaTex IR	10029-732
18" MegaTex	10029-734
18" MegaTex IR	10029-736
14" NovaPoly	10029-738
14" NovaPoly IR	10029-740
18" NovaPoly	10029-742
18" NovaPoly IR	10029-744
14" Microfiber	10029-750
14" Microfiber IR	10029-752
14" Microfiber, No Foam	10029-754
18" Microfiber	10029-756
18" Microfiber, No Foam	10029-758
18" Microfiber, No Foam, IR	10029-760
14" White Microfiber	10029-762
14" White Microfiber IR	10029-764
18" White Microfiber	10029-766
18" White Microfiber IR	10029-768

ProductionInsight

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