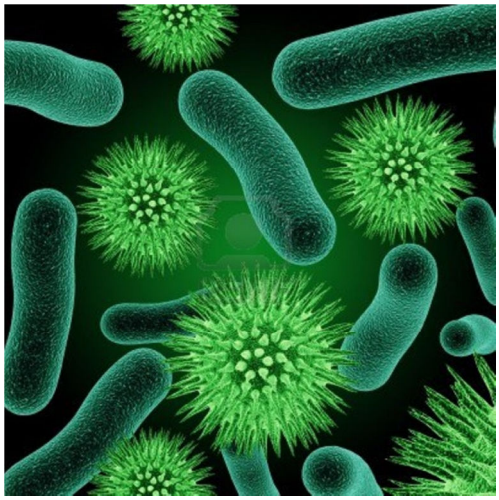

APPLICATIONS OF PULSED LIGHT FOR STERILIZATION

XENON™

History

The formal discovery that specific monochromatic wavelengths of UV light are bactericidal was made as early as 1928 (3). Since then UV lamps have been continuously developed and commercialized for a variety of sanitization and sterilization applications. The most common commercial sources of monochromatic UV light are continuous wave low and medium pressure mercury vapor arc lamps. Low pressure lamps are electrically efficient UV sources, but they are inherently low power devices (10's of watts) suitable for a very limited range of disinfection uses, are not capable of complete microbial sterilization, do not inactivate cellular repair processes, and are difficult to control in inline processes due to high output variability. Medium pressure lamps are more powerful (100's of watts), produce a wider UV spectrum, and generate sterilization levels of UV irradiance. They are constrained to an extremely limited application range, however, due to their very high operating temperatures (400 ºC – 1000 ºC), non-uniform output behavior, low electrical efficiency, and high cost (4). Finally, the extreme toxicity of mercury vapor poses a serious safety threat.

Mercury vapor arc lamp systems have undergone many engineering refinements and the technology has reached the limits of its device-physics defined performance envelope. In order to meet the growing needs in science, engineering, and industry for a better UV light source, XENON Corporation has developed and refined to maturity a new UV light source technology – the pulsed xenon arc Lamp. Superseding mercury vapor technology and its attendant limitations, XENON Corporation's pulsed xenon light source technology produces high peak power pulsed UV light, at irradiance magnitudes and dose flux rates that induce complete microbial sterilization and eliminate post-exposure repair mechanisms (5) – at ordinary operating temperatures, and with the controlled quantitative repeatability necessary for high sterility assurance level inline implementation. By utilizing controlled high irradiance UV light, delivered in short, microsecond wide pulses, at total doses on the order of 1.27 joules/cm^2, XENON Corporation's *Z-1000* systems can provide equivalent or better sterility assurance levels than conventional sterilization technologies, such as moist heat, dry heat, chemical sterilants, and gamma radiation. This performance is delivered without unwanted thermal, chemical, or ionizing radiation induced collateral damage to pharmaceutical packaging, proteins, enzymes, and antigens, and is accomplished with relatively safe, economical, and reliable equipment. Pulsed UV was approved by the FDA in 1999 for the treatment of food.

Applications Overview

All microorganisms, with the exception of Mad Cow Disease, contain DNA. Therefore, a technology that destroys DNA will provide an effective means of sanitization, decontamination and sterilization. Because high peak power pulsed UV light kills DNA and inactivates *all* types of microorganisms, including fungal yeasts and molds, bacteria, rickettsiae, mycoplasma, and viruses, it is classified as a sterilization agent. It can be used in all applications that currently utilize continuous wave UV mercury vapor arc lamps. Examples are in research (R&D) studies, surface treatment, liquids and air decontamination.

a - Research Applications

Pulsed UV is an ideal research tool for the study of the destruction of microorganisms. XENON's systems are being used in research labs around the world including United States, Canada, Spain, China and the Food Institute of Technology in Taiwan. Much of the investigative research is done in conjunction with the needs of industry.

b - Surface Applications

Pulsed UV light can be used for sanitization, decontamination and sterilization of smooth, dry surfaces such as aluminum, paper, glass, medical devices and packaging materials with implementation in clean room pass-through tunnels, and above mail conveyor belts. Additionally, pulsed UV light can be used for decontamination of rough surfaces found on food and other surfaces such as laboratory benches and inside safety hoods.

c. Liquid Applications

Pulsed UV light can be used for sanitization, decontamination, and sterilization of UV transmissive liquids, such as water, process chemicals, clear liquid pharmaceutical products, buffers, and dilute protein solutions for virus inactivation procedures.

d. Air Applications

By mounting pulsed UV lamps on walls and/or ceilings, inside heating, ventilation, and air conditioning ducts, pulsed UV light can be used for decontamination of publicly shared atmospheres in hospitals, large group living quarters, office buildings, hotels, microbiology laboratories, as well as inside contained spaces such as a sterile glove, clothing, instrument cabinets and drawers.

Material Compatibility Studies

Chemical and structural stability of items after exposure to pulsed UV light, for example pharmaceutical packaging materials, and implantable medical devices, can be determined with an investigational protocol similar to ones used for conventional sterilants such as ethylene oxide, moist or dry heat, and gamma radiation. As already emphasized, the Z-1000 employs a bench-top sterilization chamber, making it an ideal engineering development tool for determination and validation of all critical inline process operating parameters, including material compatibility, required radiant flux dose levels, optimal throughput rate, product stability, target medium effects, and sterility assurance level. Irradiation effects on materials under study are determined by controlled variation of system operating parameters. First order critical parameters that determine irradiated material stability are energy per pulse, pulse width, pulse interval, pulse quantity, spectral distribution of pulse radiant flux, and total energy deposited in the sample. All of these variables can be quantitatively controlled, monitored, measured, and recorded, with the Z-1000/R benchtop system.

Underscoring the importance of quantitative control over all critical parameters is best understood by example. Certain classes of polymers used for medical devices are damaged if exposed to 4 joules/cm^2 total dose delivered in 4 pulses at 1 joule/cm^2 per pulse, but are not damaged if exposed to 4 joules/cm^2 total dose delivered in 8 pulses at 0.5 joules/cm^2 per pulse. This energy versus time sensitivity is typical of many packaging materials which develop black spots at high energy per pulse but not at low energy per pulse.

Effective sterilization of the contents inside a container depends on transmission of short wavelength UV photons through the container walls. A good candidate for container testing is selected by choosing material with known UV transmission characteristics. Published examples of UV transmissive materials include low density polyethylene, high density polyethylene, and polyamides (nylon). In general, caution should be observed. Transparency in the visible provides no knowledge of UV transmissivity. Glass containers, for example, have excellent visible band transmissivity, but are essentially UV opaque. Quartz, on the other hand, is transmissive in both the visible and UV. Furthermore, since the mechanism of pulsed xenon UV microbial sterilization is irreversible due to photo-biochemical damage to genetic material induced by high energy UV-B and UV-C exposure in the 240 nm – 280 nm wavelength range, determination of spectral transmissivity in this range is correspondingly essential.

Microbiology Studies

A significant number of publications and presentations at scientific meetings have publicized and documented the ability of pulsed UV light to destroy microorganisms of all origins and phenotypes (1, 2 and 6). There is currently no evidence of a resistant organism. Universal lethality is accomplished by irreversible damage to nucleic acids. Some evidence has been published to support the hypothesis that a highly localized heating mechanism might cause cell death (7). It has been shown that sample temperature does increase measurably after exposure to sterilization levels of pulsed xenon broad spectrum UV light. Since proteins retain function after exposure to pulsed UV at doses that completely inactivate nucleic acids (8), it is unlikely that cell death is caused by a thermal mechanism. Given that proteins are sensitive to heat; it is reasonable that heat might play a role in cell death at dosages higher than those required for microbial sterilization.

Research Studies

XENON's model Z-1000 system affords researchers a convenient and unique tool to assist in the study of the destruction of DNA using high energy pulsed UV light. Pulsed Ultraviolet Light is a proven technology to sanitize surfaces and under certain circumstances achieves 10^6 sterility assurance levels. The high intensity pulses allow efficient transmission of the UV light through not only cell walls and membranes, but also bacillus spore coats causing irreversible damage to the nucleic acids present in the cellular material. In recent years, numerous laboratories have reported inactivation of all classes of bacteria, fungi, protozoa and virus particles. Higher efficiencies of inactivation are observed with respect to exposure time due to the peak intensity of pulsed UV delivered in microseconds as compared to conventional UV light that requires significantly longer exposure times to deliver an equivalent amount of energy. Pulsed UV is an excellent replacement of conventional mercury UV lamps for decontamination of food, water, and related packaging. Pulsed UV is an excellent technology to reduce the probability of the spread of microorganisms including virus particles by surface contact. It is used in worldwide research facilities, including the following:

- AINIA Centro Tecnologico, Laboratorio de Bioensayos, Valencia, Spain
- Alabama A&M
- American Red Cross Holland Laboratories
- Collage of Food Science – Fugian Agriculture and Forestry University, China
- Cornell University
- Florida Dept. of Citrus
- Fort Valley State University
- Georgia State University
- Institute of Food Technology – Taiwan
- McGill University
- Nissan Pharmaceuticals
- Nutramax Corp
- Pennsylvania State University
- Rutgers University
- University of Massachusetts
- U.S. Department of Agriculture

Model viruses that have been tested with Pulsed UV:

- SV40
- Canine Parvovirus
- Porcine Parvovirus
- Simian Rotavirus (SA11)
- Bacteriophage PRD-1
- Poliovirus Type I
- Reovirus
- Bacteriophage MS-2
- Encephalomyocarditis Virus (EMC)
- Hepatitis A Virus
- Human Immunodeficiency Virus (BVDC)
- Sindbus Virus
- Vaccinia Virus
- Vesicular Stomatitis Virus

Experimental Results Using the Z-1000 on *Bacillus subtilis* Spores

The high peak power pulsed UV light generated by XENON Corporation's model Z-1000 system has been experimentally proven to inactivate microorganisms, including bacterial endospores, which are known to be extremely resistant to radiation and other physical and chemical agents. In one exemplary study, Dr. Abraham Sonenshein at Tufts University demonstrated the system's effectiveness by irradiating *Bacillus subtilis* spores with pulsed UV light generated by the SteriPulse-XL system. Dr. Sonenshein's report demonstrates that the number of surviving spores decreased in each sample after irradiation. The sample with population of 10^7 spores per ml decreased below the detection limit after three pulses. Similar results were obtained on the sample with 10^8 spores per ml. As expected on the basis of geometrical shadowing at very high concentration, the sample containing 10^9 spores per ml was not completely inactivated. In this regard it should be noted that validation studies for the medical device and pharmaceutical industries use concentrations of 10^7 or less per ml.

Bacillus spores are used to validate medical devices and pharmaceutical products as surrogates because these spores are more resistant than all other types of microorganisms. Successful inactivation of *Bacillus subtilis* spores

proves the Z-1000 system to be an effective sterilization technology.

Sanitizing Surfaces

Pharmaceutical and medical device companies are increasingly manufacturing their products in clean rooms equipped with two types of enhanced clean room devices. One device is the simple hood or flow cabinet, the second is a fully enclosed clean work environment known as the isolator or barrier isolator. The common feature of clean room devices is the increased separation of the manufacturing activity from the human clean room technician. A key function of clean room devices is to control microbial contamination near and within the manufacturing area. This is accomplished by air flow through HEPA filters and the construction of walls or barriers. The ultimate success of the clean room device depends upon the ability to transport materials into and out of the clean work environment without the introduction of microbial contamination. Xenon Pulsed UV Light Systems are designed to work in these clean room devices and control microbial contamination.

Completely enclosed barrier isolator manufacturers have designed transfer ports to move material into the isolator while controlling the introduction of microbial contamination. The transfer ports are designed differently than conventional transfer hatches or airlocks. The transfer ports are increasingly equipped with a method to sterilize the surface of materials entering the isolator and to allow a rapid transfer of materials. Systems equipped with slow acting vapor phase hydrogen peroxide or conventional UV light are being displaced with the more rapid decontamination agent, pulsed UV light, that is capable of sterilizing the surface of materials in seconds without significantly increasing the temperature in the chamber. Pulsed UV light systems also sterilize the empty transfer port after each use. No vapor or gaseous decontamination chemical is used or introduced into the clean room.

Completely enclosed barrier isolators and open isolators (hoods) must be decontaminated before and after each use as a clean work environment. Common methods employed by industry include vapor phase hydrogen peroxide, ozone based procedures, liquids such as Peracetic acid or hydrogen peroxide. These systems normally are validated to achieve a 3-6 log kill to meet most application regulatory requirements. Each method requires the surface to be cleaned prior to applying the decontamination chemical. Pulsed UV light is an acceptable alternative that can be applied in seconds without labor and does not involve the introduction of a gaseous chemical or create a toxic waste. Pulsed UV light applications are fully automated and designed as an integral component of the system, eliminating the potential introduction of human-borne microbial contamination.

As clean room technology advances to automation and further isolation of the work environment, equipment and system design should consider the application of pulsed UV light as a safe and effective method to decontaminate surfaces in less than a second without the use of a gaseous or liquid toxic chemical. Pulsed UV light systems do not cause a significant increase in surface temperature and do not generate waste products.

References

1. Cover, W. 1999. "*Advanced technology for rapid sterilization of pharmaceutical products, medical devices, packaging and water*." PurePulse Technologies, Inc. Press, San Diego.

2. Dunn, J. 2001, "*Pulsed light disinfection of water and sterilization of blow/fill/seal manufactured aseptic pharmaceutical products*"; in *Disinfection, Sterilization, and Preservation,* Seymour S. Block, editor, Lippincott Williams & Wilkins; pp. 765-793.

3. Gates, F. L. 1928. "*On nuclear derivatives and the lethal action of UV light*." Science, 68, 479-480.

4. Blatchley, Ernest R. III and Peel, Margaret M. "*Disinfection by Ultraviolet Radiation.*" In *Disinfection, Sterilization, and Preservation*. Edited by Seymour S. Block, Philadelphia: Lippincott Williams & Wilkins, Fifth Edition, 2001. Page 828.

5. Furukawa M, Enta N, and Kawamata T. 1999. "*Brand new pulsed light sterilization technology can sterilize both injectable solution and its 20 ml polyethylene container*", Proceedings of the 1999 PDA International Congress, Courses and Exhibition.

6.Wallen, D., R. May, K. Rieger, J. Holloway, and W. Cover 2001. *"Sterilization of a New Medical Device Using Broad-Spectrum Pulsed Light."* Biomedical Instrumentation and Technology, September/October 2001, 327-328.

7. Wekhof, A. 2000. "*Disinfection of Flash Lamps*", PDA J. Pharm. Sci. & Tech. 54(3): pp. 264-275.

8. Cover, WH, JM Holloway, H Xue and TF Busby 2001. "*Inactivation of lipid enveloped and non enveloped viruses in human plasma proteins with Broad Spectrum Pulsed Light*". Downstream, PPB 2001 Abstracts. pp. 42-45.

Further Reading

1. Dunn, J. 1998. "*PureBright pulsed light sterilization*." pp. 393-431. In F. M. Nordhauser and W. P. Olson, "*Sterilization of drugs and devices*", Interpharm Press Inc., Buffalo Grove, Illinois.

2. Wallen, RD, R. 2001, May, K, Reiger, JM Holloway, and WH Cover; "Sterilization *of a new medical device using broad spectrum pulsed light*." Biomedical Instrumentation and Technology; 35; pp 323-330.

3. Woodling, Sarah E and Moraru, Carmen I. "*Influence of Surface Topography on Effectiveness of Pulsed Light Treatment for the Inactivation of Listeria innocua on Stainless-steel Surfaces*; Journal of Food Science, Vol. 70, Nr 7, 2005

XENON™
The Pulsed Light Experts

XENON Corporation
37 Upton Drive
Wilmington, MA 01887-1018

Telephone 978-661-9033
Toll Free 800-936-6695 (U.S.A. Only)
Fax 1-978-661-9055
www.xenoncorp.com