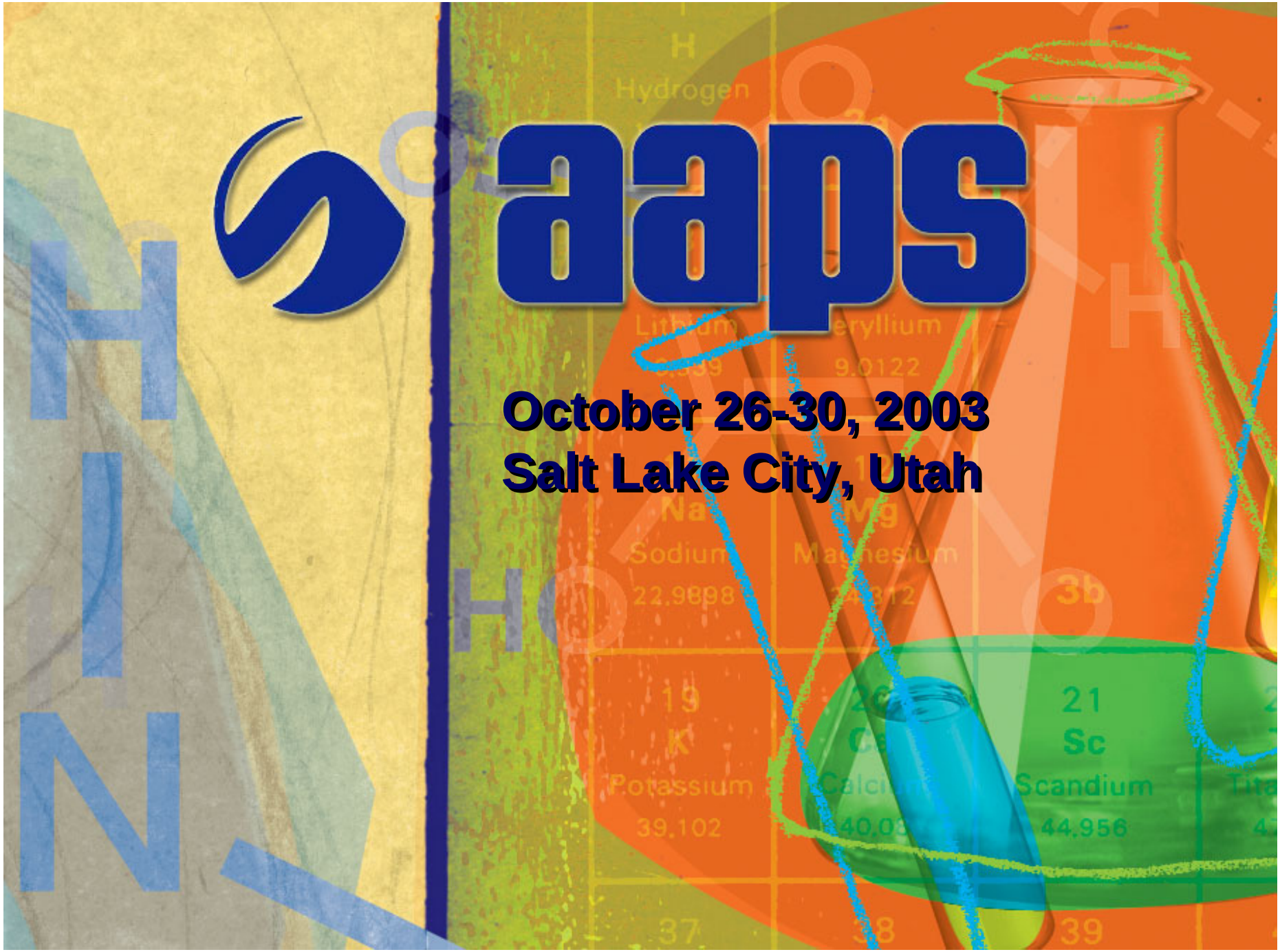

aaps
October 26-30, 2003
Salt Lake City, Utah

High Energy Pulsed UV Light as a Sterilization Process

American Association of Pharmaceutical Scientists – Annual Meeting and Exposition

October 27, 2003

Presented by

Louis Panico, CEO

UV Sources

- Basic techniques to generate UV light
  - Continuous
  - Pulsed
- Sources of plasma-generated UV radiation
  - Electric arc
  - Mercury lamp
  - Pulsed xenon flashlamp

XENON

Conventional UV vs. Pulsed UV

Conventional UV

- Mercury lamp
- Monochromatic light - 254nm
- Long exposure times
- Generates heat
- Repair of DNA dimers
- Not capable of sterilization
- Loss of energy from lamp during continuous emission

Pulsed UV

- Xenon inert gas
- Broad spectrum - 200-1100 nm
- Very short exposure time (seconds – minutes)
- No significant heat generated
- DNA strand breakage--No evidence of repair mechanism
- Achieves USP sterility levels
- No loss of lamp energy between pulses

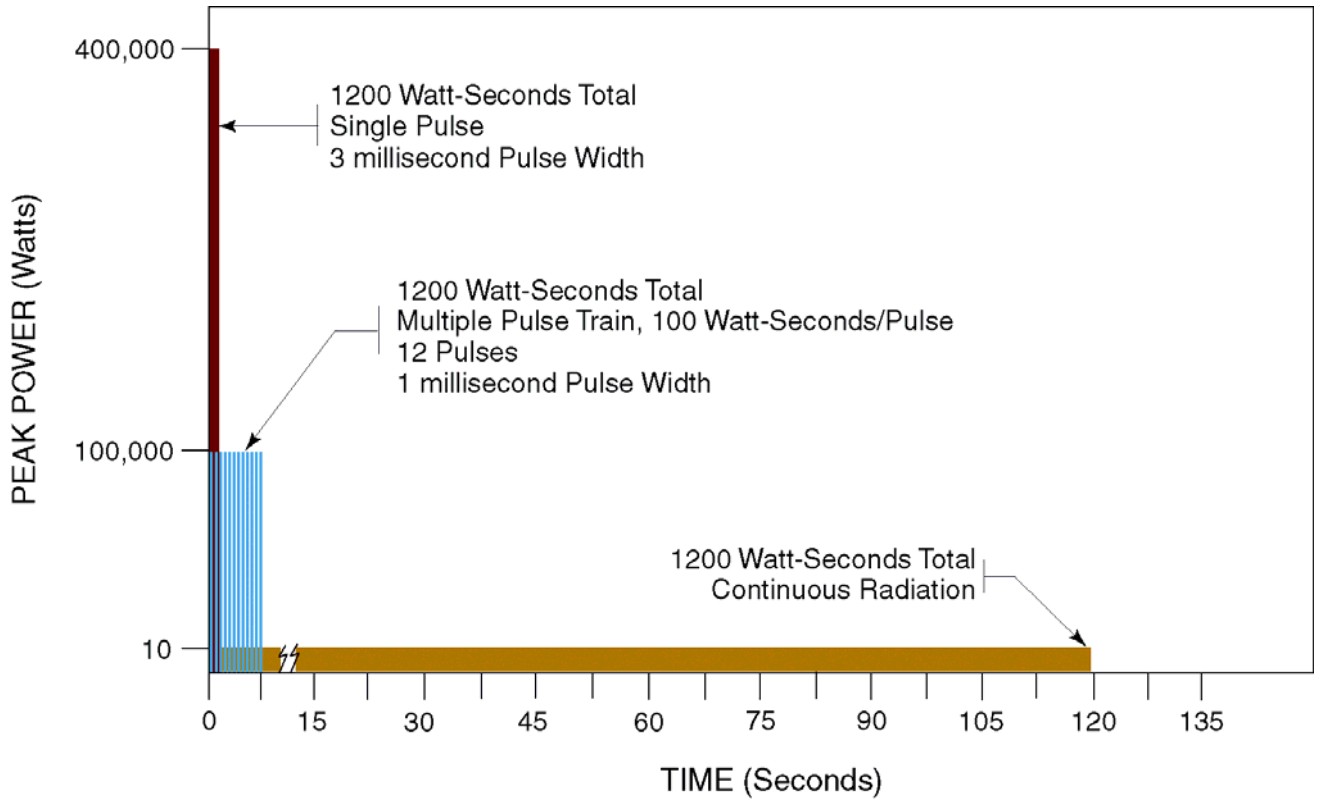
XENON

Why Pulsed UV Light?

- Generates wideband radiation – 50 nm to 5 microns
  - Especially rich in UV spectral region 180 nm to 400 nm
- Highly efficient for UV light generation
  - 50% to 60% of input electrical energy converted to optical energy
- Environmentally benign
  - Does not use toxic materials such as mercury
  - Does not create suspended airborne particulates
- Pulsed UV systems provide unique attributes
  - Very high peak power .. As high as 1×10^6 watts
  - Low surface temperature buildup
  - Instant on/off control
  - Multishaped lamps match application requirements

XENON

Comparison of Pulsed UV and Continuous UV



Pulsed light is illustrated in a single pulse and burst mode

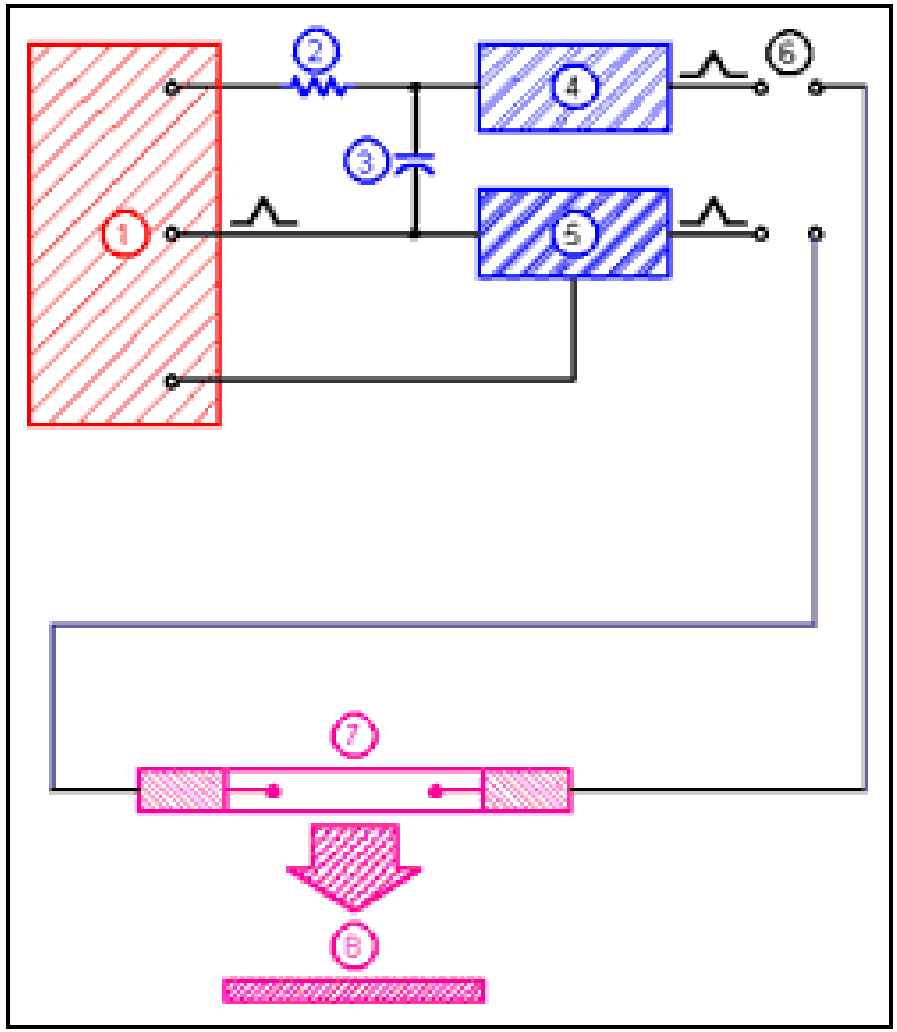
XENON

Pulsed UV
System components

- High voltage power supply
- Pulse forming network (PFN)
- Flashhead module
  - Incorporates UV optics
- Blower or cooling system for flashhead module
  - Effectiveness will determine operation and life of the UV source
- Control Module

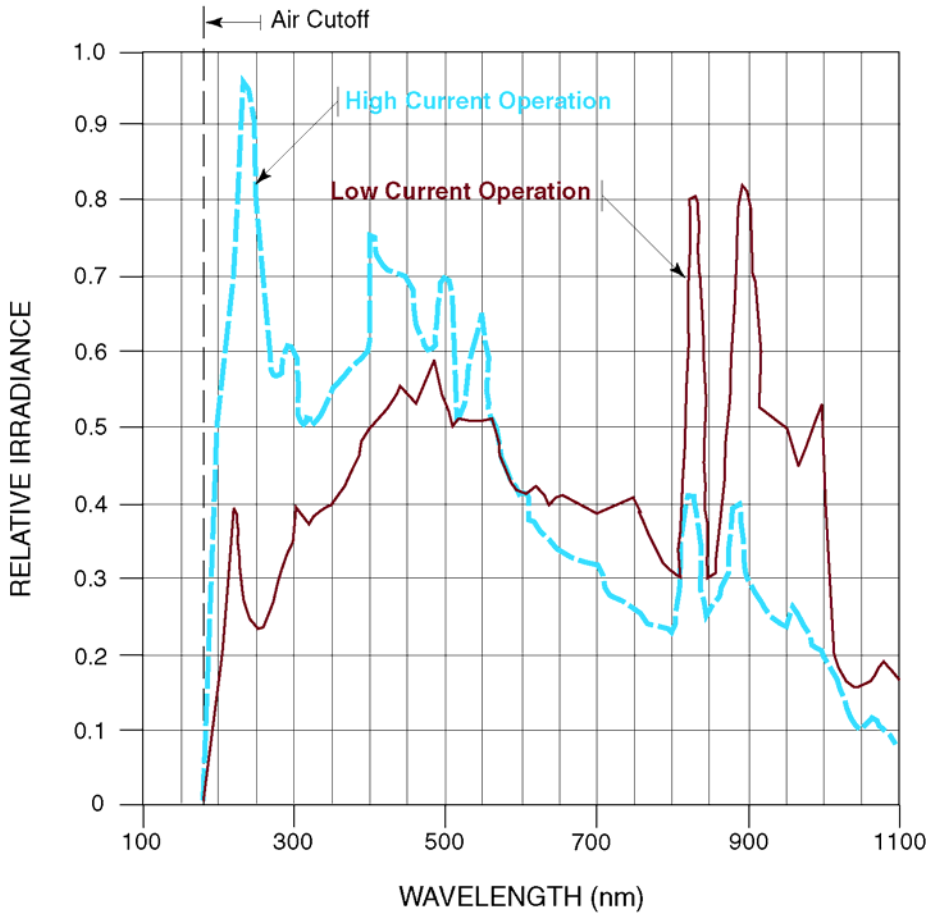
XENON

Block Diagram
- Pulsed UV Light System



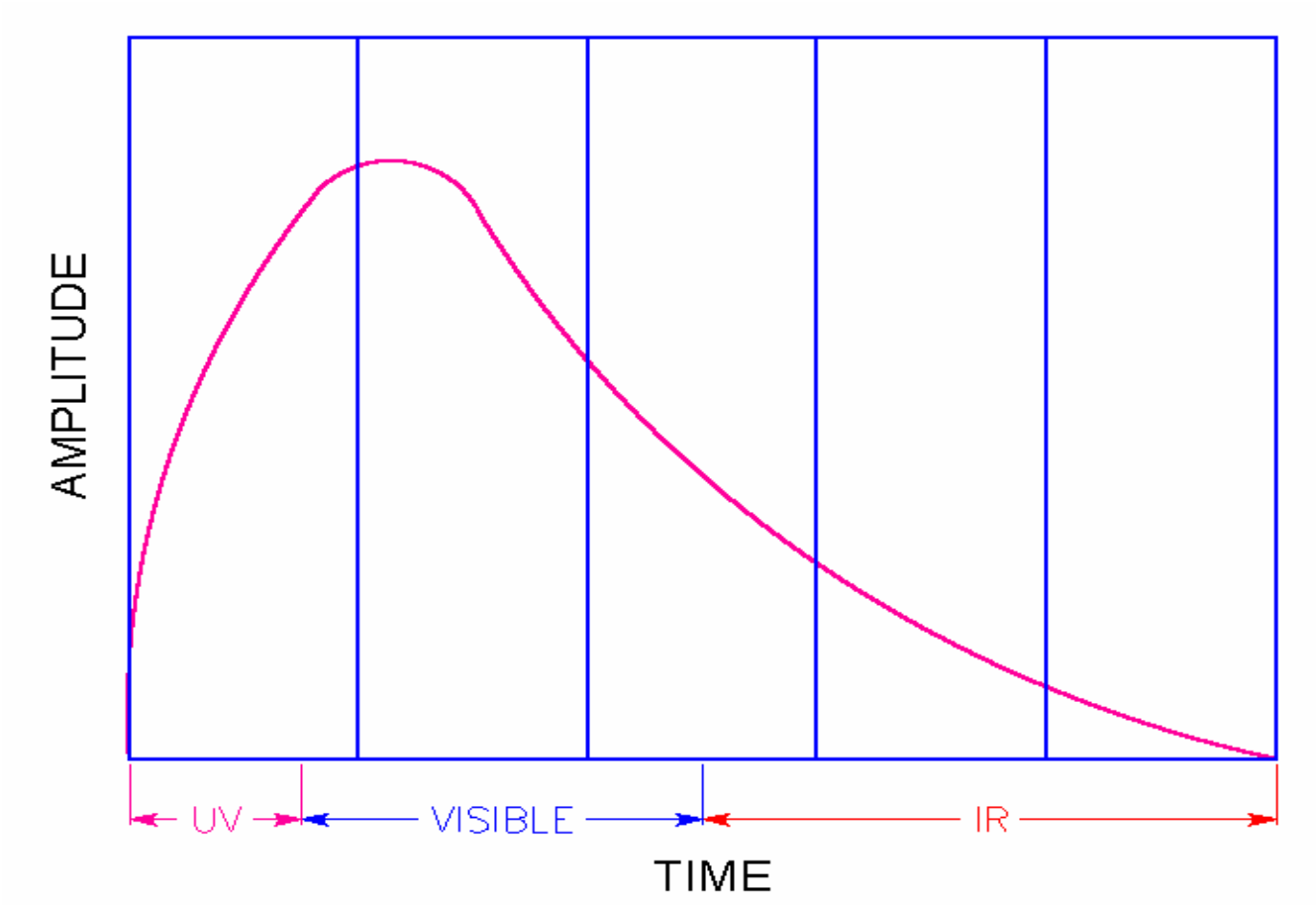
XENON

Spectral Dependence on flashlamp operating parameters



XENON

Spectral Components - a single pulse of light



XENON

Pulsed UV Exposure - effects on microorganisms

- Provides effective means of photophysical and photochemical reactions of light absorption by molecules
- Produces chemical pathways such as short-lived chemical species, charge-transfer reactions and energy transfer phenomena in chemical biological systems
- Primary process in sterilization of microorganisms is by destroying DNA and RNA

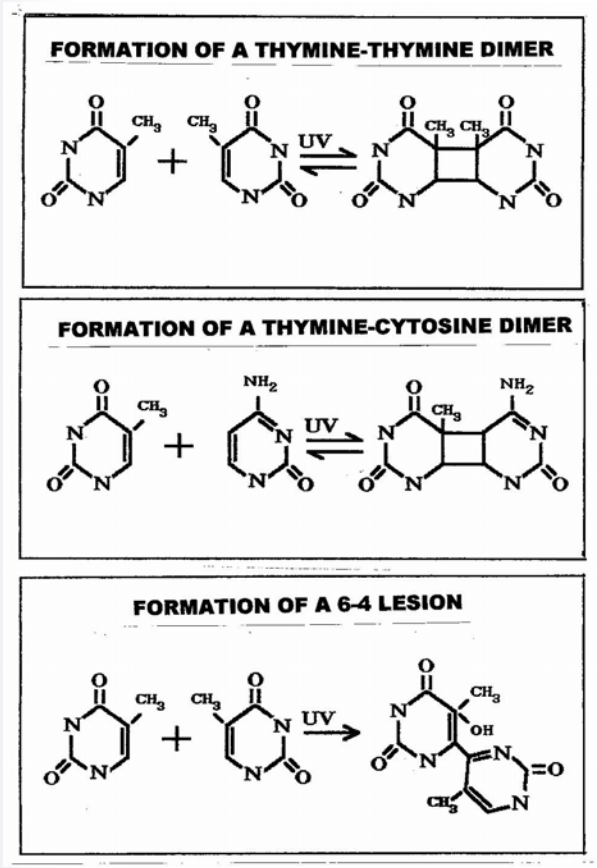
XENON

Mechanisms of Action of Pulsed UV

- DNA: Demonstration of strand breaks and dimer formation in vivo and vitro
- RNA: Single stranded breaks and formation of dimers
- Proteins: Peptide bonds not broken; Inactivation of enzyme activity controlled or minimized by controlling the delivery of critical parameters
- Membrane Effects: Under investigation using platelets and bacteria as model systems.

XENON

UV Exposure
- Formation of Dimers and 6-4 Lesions

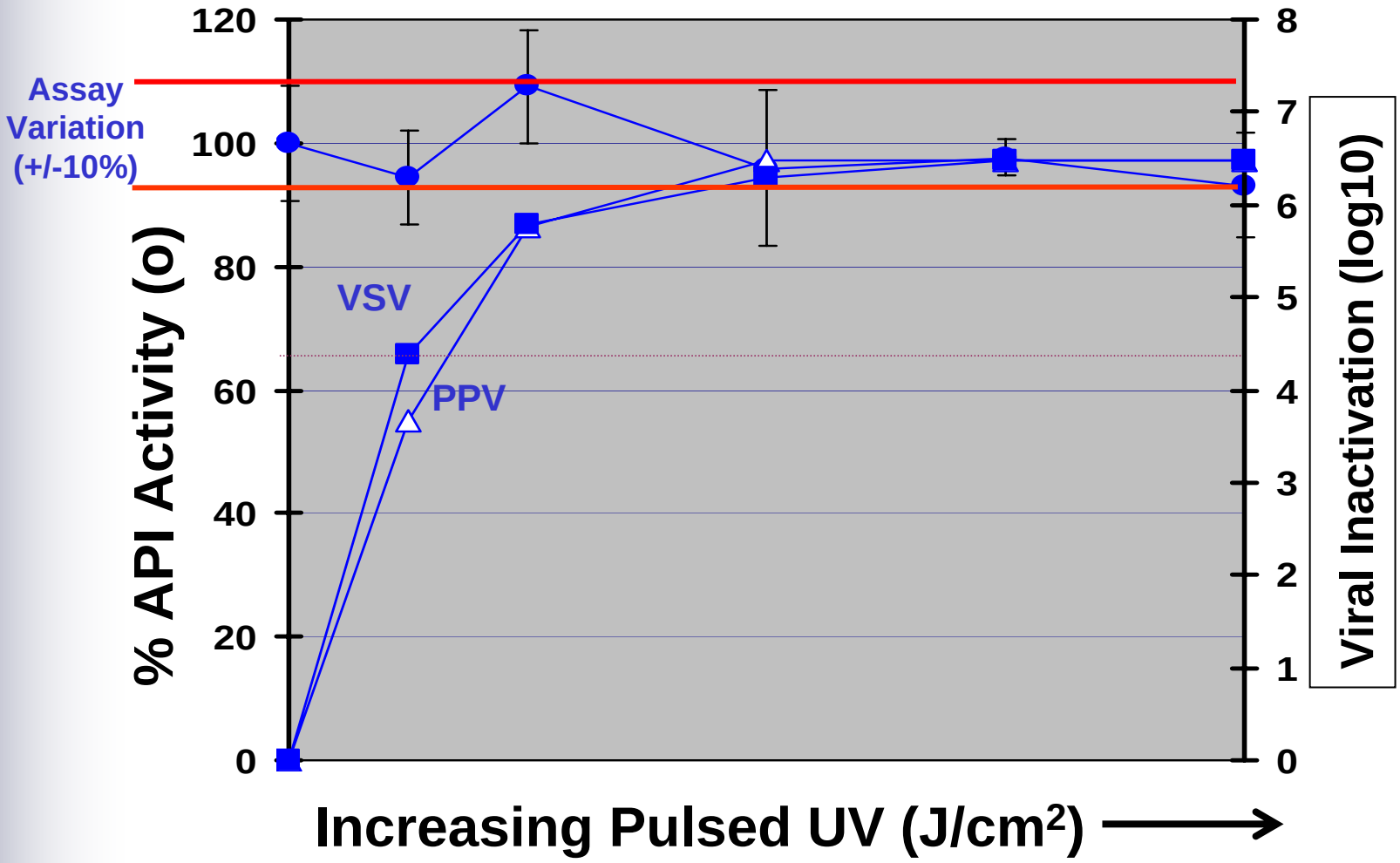


- DNA damage caused by UV exposure includes formation of pyrimidine dimers and (6-4) photoproducts
- These damages result in mutations, impairment of replication and gene transcription – leading to the death of the organism
- Cells have evolved mechanisms for repairing DNA damage
- Pulsed UV radiation leads to ultimate genetic destruction of microorganisms
  - Ability to adjust light intensity
  - Ability to adjust pulse duration
  - Ability to select number of pulses

XENON

>6 Log Non-Enveloped Virus Reduction

Showing Complete Recovery of API After Exposure to Pulsed UV



XENON

Opportunities with Pulsed UV

- Virus Inactivation of enveloped and non-enveloped viruses
- Decontamination of high purity water systems
- Terminal sterilization of Blow/Fill/Seal containers
- Terminal Sterilization of medical devices and packaging arrangements

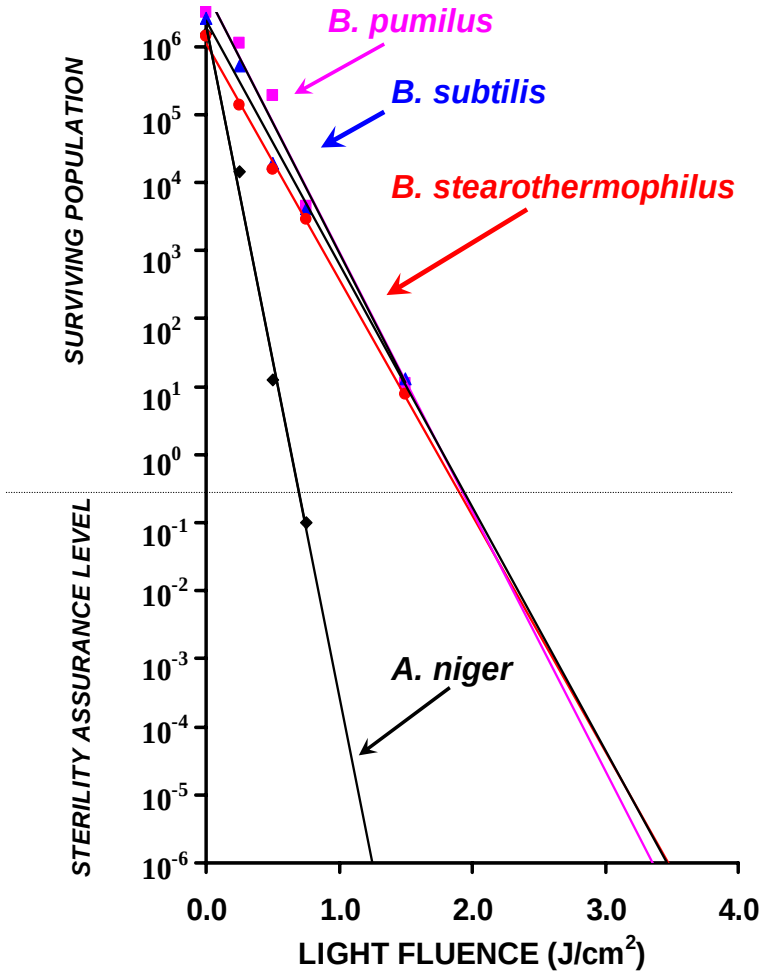
XENON

Surface Sanitization
- results from tests on bacteria spores

- Pulsed UV light has been shown to be effective in applications requiring surface sanitization
- Tests performed on spores using Pulsed UV
  - Type produced by Bacillus and Clostridium species
  - Known to be resistant to various forms of radiation and other physical & chemical agents
  - Spore samples irradiated with pulsed UV light

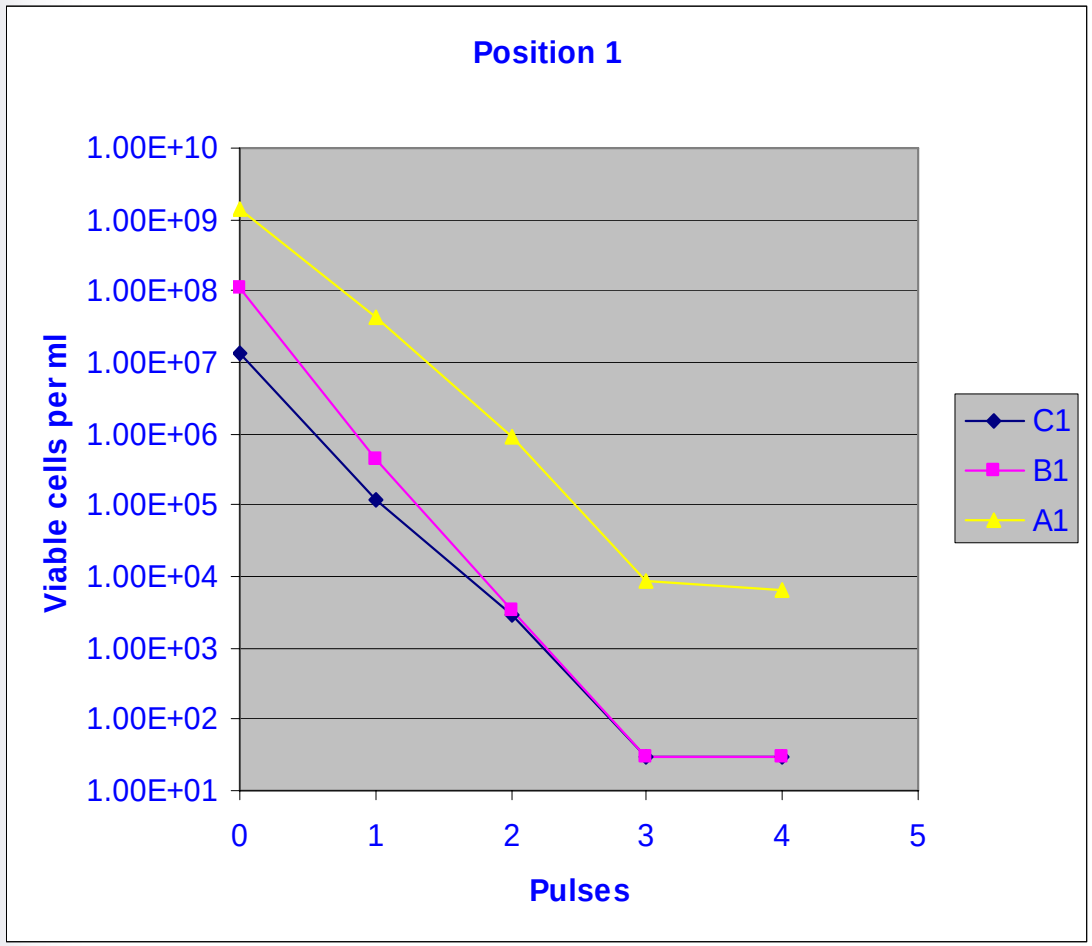
XENON

Dry Surface Survival Kinetics



XENON

Viability of *bacillus subtillus* spore samples exposed to UV pulses



Samples located on the flashlamp axis and at the mid point of the flashlamp

Figure provided by Abraham L. Sonenshein, PhD
Department of Molecular Biology and Microbiology
Tufts University School of Medicine

XENON

Sterilization of Static Liquids in 20 ml BFS Vials

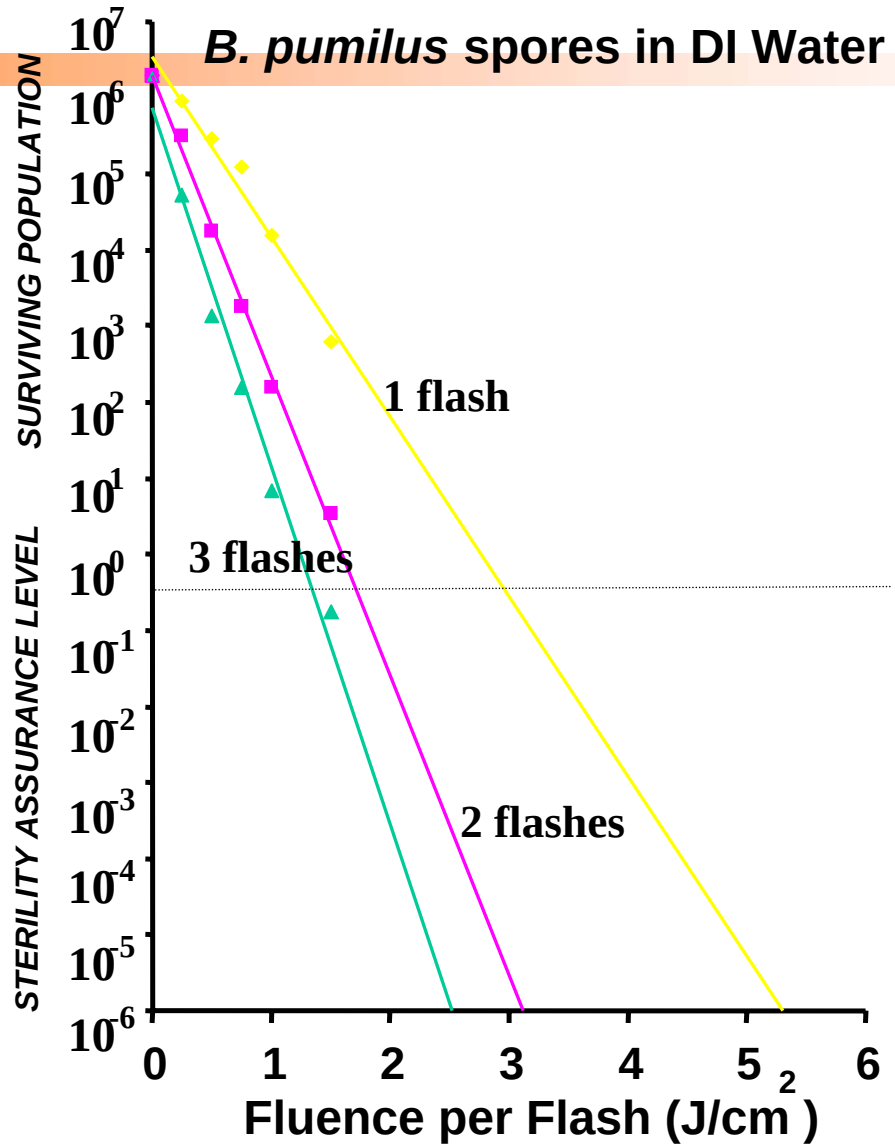
Organism	Inoculation (in 20 mL)	Sterility Test Result [1]		
		Glucose	Saline	WFI
Bacillus subtilis var. niger spores	4.8 x 10	Pass	Pass	Pass
Bacillus pumilus spores	3.0 x 10	Pass	Pass	Pass
Bacillus stearothermophilus spores	4.4 x 10	Pass	Pass	Pass
Clostridium sporogenes spores	2.4 x 10	Pass	Pass	Pass
Aspergillus niger spores	1.4 x 10	Pass	Pass	Pass
Candida albicans	3.0 x 10	Pass	Pass	Pass
Deinococcus radiodurans	2.2 x 10	Pass	Pass	Pass
Staphylococcus aureus	5.6 x 10	Pass	Pass	Pass
Enterococcus faecalis	2.0 x 10	Pass	Pass	Pass
Escherichia coli	3.4 x 10	Pass	Pass	Pass
Salmonella choleraesuis	1.8 x 10	Pass	Pass	Pass
Pseudomonas aeruginosa	2.8 x 10	Pass	Pass	Pass

[1] Treatment level was approximately 4.5 J/cm^2 per flash, with 2 flashes. 20 replications for each liquid/microbe combination. No dark or light enzymatic repair of nucleic acids after 28 days of incubation.

Reference: Furukawa et al., Japanese PDA, 1999

XENON

Static Liquid Survival Kinetics



XENON

Model Viruses 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 (HIV-1)

Bovine Viral Diarrhea Virus (BVDV)

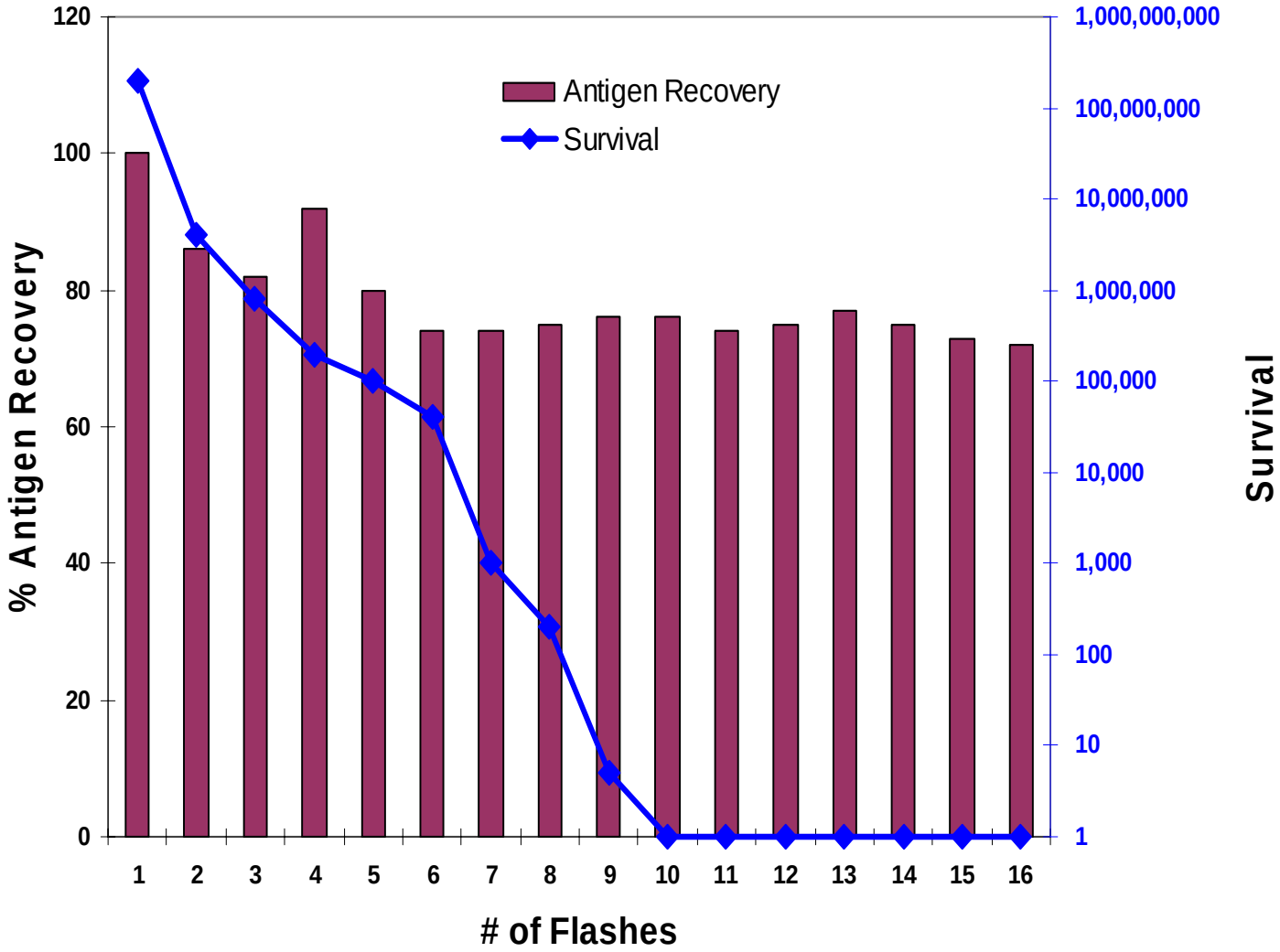
Sindbus Virus

Vaccinia Virus

Vesicular Stomatitis Virus

XENON

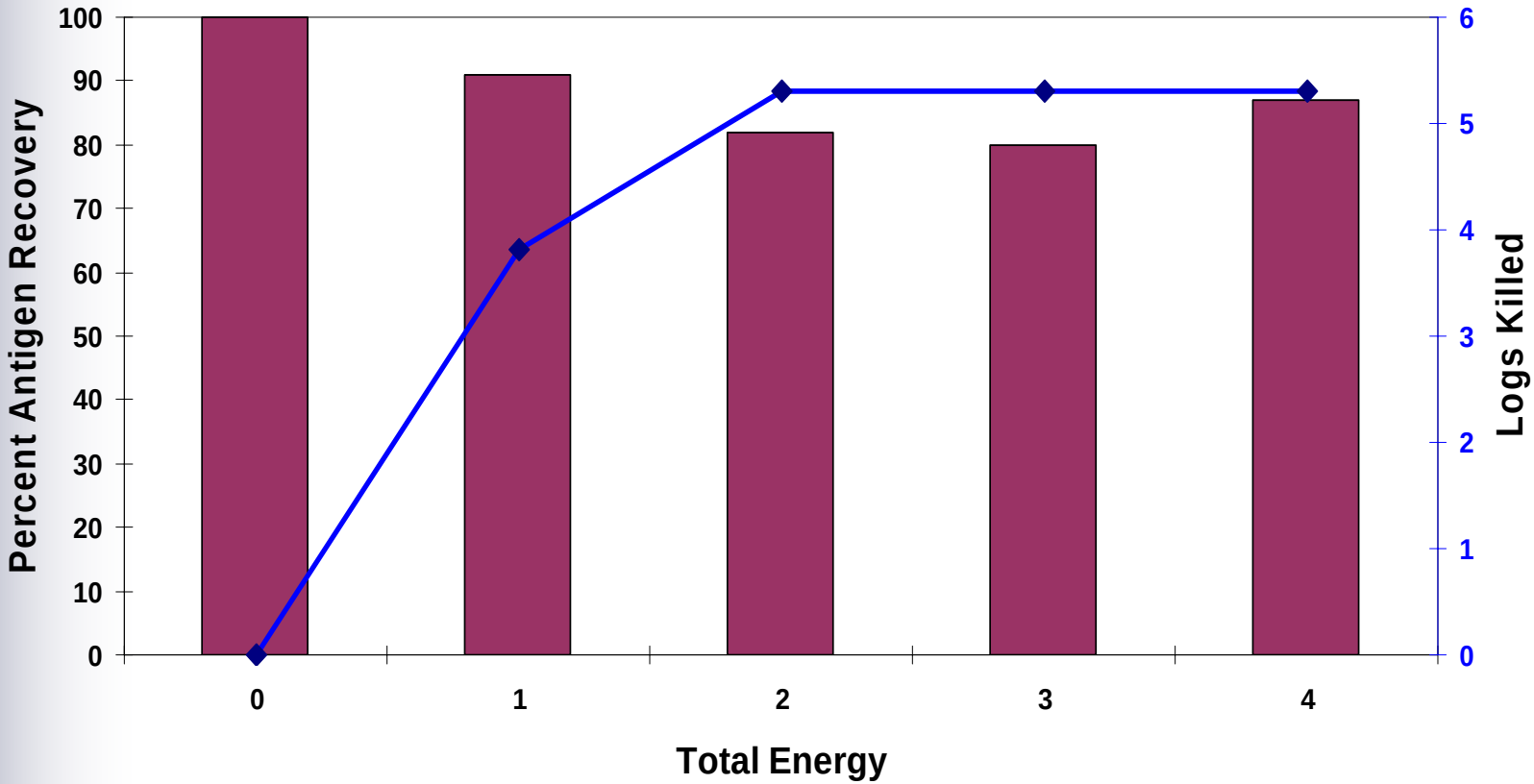
Pulsed UV Demonstrates Complete Inactivation of a Cancer Causing Virus with High Antigen Recovery



XENON

Complete Inactivation of Herpes Simplex Virus I with High Antigen Recovery

Reproduced courtesy of Dr. David Katz, Univ. of Georgia State



XENON

Validatable with Real Time In-Process Monitoring

- **UV and full spectrum (FS) monitors**
  - **FS fluence (lamp and product)**
  - **UV fluence (lamp and product)**
  - **Transmission**
- **Error checking**
  - **Product flow rate**
  - **Lamp current**
  - **Load cell force**
  - **Flash rate**
- **Product temperature**

XENON

Regulatory Status of Pulsed UV

- In-line sterilization of thin films for producing IV bags
  - **Cleared by FDA for production**
- Terminal sterilization of interstitial space of packaging arrangement
  - **In production in Canada**
- Terminal sterilization of blow/fill/seal parental diluents
  - **In production in Japan for over 3 years**
- Terminal sterilization of microchip implant device
  - **Phase III clinical trial in USA**
- Barrier isolator device undergoing validation in Europe
- Laboratory scale in-flow virus inactivation device undergoing validation in treating plasma derivative products

XENON

Application of Pulsed UV
-implantable medical device production

- Ease of integration into automated manufacturing environment
- Example shown : complete curing of a lubricious coating on medical guide wires

Photo courtesy Guidant Corporation

XENON

Terminal Sterilization - Syringe

Pulsed UV Summary

- **EFFECTIVE INACTIVATION**
  - Achieve USP 10^{-6} SAL
  - No microorganism found resistant to Pulsed UV
  - No repair of nucleic acids
- **SELECTIVE BIOMOLECULAR DESTRUCTION**
  - Destruction of DNA/RNA
  - High antigen recovery
  - No significant heat effect on product
- **RAPID & CONTROLLED PROCESS**
  - Single step process
  - Treatment in <u>minutes</u> (per liter)
  - Broad spectrum fluence monitoring
- **SAFE**
  - No toxic chemicals or ionizing irradiation
- **SCALABLE**
  - 200 ml/min to >10 L/min.

XENON