



Gail Sofer

Both the process and the product strongly influence viral inactivation, and unknown or unspecified details — such as variability in virus titers, measuring devices, calibrations, and protocols — can all influence log reduction values. This article series covers what you need to know to fully understand the properties of the test article, the viruses inactivated, and the critical control parameters for selected inactivation methods.

A member of BioPharm International's editorial advisory board, **Gail Sofer** is director of regulatory services at BioReliance, 14920 Broschart Road, Rockville, MD 20850-3349, 301.738.1000, ext. 2580, fax 301.610.2590, gsofer@bioreliance.com, www.bioreliance.com.

Virus Inactivation in the 1990s — and into the 21st Century

Part 5, Disinfection

FDA regulations require validated viral clearance of biopharmaceutical products. Yet the potential viral contaminants, the media, and the protein make inactivation unique. So it is important for researchers to know what inactivation methods have already been tried. This article series addresses that concern with information compiled from an extensive literature search on viral inactivation. The results of that search are presented in an organized manner — by skin, bone, and cells (1); red blood cells and platelets (2); plasma and plasma products (heat and solvent/detergent treatments) (3); plasma and plasma products (treatments other than heat and solvent/detergent) (4); and culture media, biotechnology products, and vaccines (5).

This article covers disinfection as a stand-alone topic because of the importance of making equipment and components, such as chromatography resins, safe for subsequent use after possible contact with viruses. This point has been repeatedly emphasized by

regulatory authorities, and it is also critical to ensuring worker safety when dealing with high-risk materials.

A *disinfectant* has been defined as “an agent that frees from infection; usually a chemical agent that destroys disease germs or other harmful microorganisms or inactivates virus” (6). In this article, disinfectants targeted to specific viruses are discussed first, followed by specific approaches reported in the literature for disinfection in plasma and culture media. The full name of viruses abbreviated in this article can be found in the “Virus Abbreviations” sidebar, along with whether those viruses are enveloped or not.

General Methods of Disinfection

A variety of disinfection methods are targeted to specific viruses, including the use of high hydrostatic pressure, hydrogen peroxide, and ultraviolet (UV) light; bleach and other chlorine compounds; glutaraldehyde, ethanol, and metal ions; quaternary ammonium compounds; and

Virus Abbreviations

Abbreviation	Virus	Enveloped	Not Enveloped
ADV	Adenovirus		√
BVDV	Bovine viral diarrhea	√	
CMV	Cytomegalovirus	√	
CPV	Canine parvovirus		√
DHBV	Duck hepatitis B virus	√	
FCV	Feline calicivirus		√
HAV	Hepatitis A virus		√
HBV	Hepatitis B virus	√	
HIV	Human immunodeficiency virus	√	
HSV	Herpes simplex virus	√	
PRV	Pseudorabies virus	√	
RSV	Respiratory syncytial	√	
SVDV	Swine vesicular disease virus	√	
VSV	Vesicular stomatitis virus	√	

sodium hydroxide or sodium carbonate, among a few others.

High hydrostatic pressure. At more than 300 MPa for 10 minutes at 25°C, HSV was reduced by more than 7 log₁₀, and CMV was reduced by more than 4 log₁₀. The HSV and CMV virus envelopes were damaged. This technology was investigated for use in the food processing industry at moderate temperatures (7).

Hydrogen peroxide. Microaerosolized hydrogen peroxide (5%) mist completely inactivated the viral poultry pathogen infectious laryngotracheitis virus, Newcastle disease virus, infectious bronchitis virus, and avian influenza virus showed reduced infectivity but were not completely inactivated. Avian reovirus susceptibility varied with the exposure method, and infectious bursal disease virus was highly resistant. At a 10% concentration, however, the hydrogen peroxide mist inactivated even the infectious bursal disease virus (8).

UV. HIV inactivation by UV light was investigated and found to be dependent on the strength of the UV light and on the composition of the medium in which HIV was contained. Cell-free HIV suspended in medium was inactivated after 10 minutes and cell-associated HIV after 30 minutes. But exposure of up to 60 minutes did not completely inactivate cell-associated HIV in the presence of blood (9).

Bleach and other chlorine compounds. HSV was inactivated by 0.01–0.02% bleach (sodium hypochlorite, NaOCl). Bleach was found to be more effective for HSV inactivation than 50% ethanol (10). At exposure ≥ 30 seconds, HIV-1 was completely and consistently inactivated by undiluted household bleach. Inactivation was inconsistent at exposure times of 15 and 25 seconds. A 10% dilution of bleach did not inactivate HIV even after five minutes of exposure (11). Total inactivation of VSV on a hydrocolloid dental impression was achieved by three to 20 minutes exposure to 0.5% sodium hypochlorite (12).

Chlorine dioxide inactivated HIV-1 in the presence of blood and medical supplies such as plastics and paper in medical waste processing (13). Chlorohexidine gluconate coated onto latex gloves was found to rapidly inactivate a model retrovirus, HSV, and HBV by 90–100% (14).

Glutaraldehyde at $\geq 0.1\%$ was effective against purified poliovirus at pH 7.2 when

Table 1. Data from review of HIV inactivation by various disinfectants, including information on plasma and various plasma products (23)

Disinfectant	Concentration (percentage)	Contact Time (in minutes)	Test Article	Inactivation (log ₁₀ reduction)
Sodium hypochlorite	0.5	1, 5	50% plasma	>7.0
β -propiolactone	0.14	240	4% gamma globulin	>4.5
Ethanol	70	1, 5	50% plasma	>7.0
Chloroform	water-saturated	15–240	lyophilized FVIII	0
Quaternary ammonium compound-1 ^a	0.08	1	50% plasma	<6.0
	0.08	10	50% plasma	>7.0
Nonidet p-40	0.5	1,5,10,15	50% plasma	>8.0
TNBP plus sodium cholate in varying concentrations	0.3	150	FVIII concentrate	>4.5
	0.2	150	FVIII concentrate	>4.5
	0.3	20–300	FVIII concentrate	>2.5
	0.2	20–300	FVIII concentrate	<2.5

^a 1.536% octyldecyldimethyl ammonium chloride, 0.768% dioctyldimethyl ammonium chloride, 0.768% N-dioctyldimethyl ammonium chloride, and 12.288% alkyldimethylbenzyl ammonium chloride

assayed by a suspension procedure. Glutaraldehyde's inactivating capabilities were increased at alkaline pH, but at acid pH it was ineffective. Glutaraldehyde was not effective at concentrations up to 1% at pH 7.2 when measured by inactivation assays on polio RNA (15).

Glutaraldehyde (2%) totally inactivated VSV on a hydrocolloid dental impression in less than one minute (12). A 2% solution of glutaraldehyde was demonstrated to effectively disinfect solid surgical instruments, as determined by a DHBV assay (16).

Enteroviruses used to test the efficacy of disinfectants for medical devices included two wild type strains. The wild type strains showed less sensitivity to glutaraldehyde than the reference strain of echovirus type 25 JV-4 and polio (17).

Ethanol. Disinfection using 70% ethanol was evaluated for HIV in suspension and HIV dried onto surfaces in the presence of both high and low concentrations of protein. In suspension, high titers of HIV were inactivated rapidly regardless of protein load. When the virus was dried onto a glass surface, however, the rate of inactivation decreased when high levels of protein were present (18).

Metal ions. Copper (II) and iron (III) ions were shown to inactivate five enveloped or nonenveloped, single- or double-stranded DNA or RNA viruses. Adding peroxide enhanced the effectiveness of the ions in a procedure intended for liquid disinfection of

medical devices. Mixtures of copper (II) ions and peroxide were more effective than glutaraldehyde. Viruses used were Φ X174, T7, HSV, Φ 6, and Junin (19).

Quaternary ammonium compounds and sodium hydroxide or sodium carbonate.

Didecyldimethylammonium chloride (DDAC, 0.1%) with 0.1 N sodium hydroxide (NaOH) was somewhat effective in inactivating SVDV. At 4°C, greater than 3.1 log₁₀ were inactivated after two hours (20). Data for HAV inactivation with 0.1% DDAC and 0.1 N NaOH indicate log₁₀ reduction factors of greater than 3.8 and greater than 5.3 (21).

In a study on decontamination of stainless steel surfaces, FCV was not effectively inactivated at concentrations recommended by the manufacturer of a combination disinfectant consisting of a quaternary ammonium compound and sodium carbonate. At twice the recommended concentration, however, it completely inactivated FCV. (22).

Other disinfectants and reviews. A thorough review of disinfectant inactivation of HIV was published in 1991 (23). Cytopathic effect (CPE) and p24 antigen were measured to assess the effectiveness of glutaraldehyde, phenolics, iodine, chlorine, quaternary ammonium compounds, and ethanol in inactivating cell-free and cell-associated HIV. The data are presented in Table 1. Cell-associated HIV was more resilient. The presence of blood also decreases the efficacy

Table 2. Data from two studies on HAV inactivation by NaOH (21, 27)

NaOH (M)	Temperature (°C)	Time (minutes)	Log ₁₀ Reduction
0.1	60	2	complete
0.1	25	120	incomplete
0.25	60	30	incomplete
0.5	4	120	incomplete
1.0	15	—	incomplete

of disinfectants. Cell-associated HIV in whole human blood was completely inactivated by glutaraldehyde, iodine, and 75% ethanol after one minute and by hypochlorite after a 10-minute exposure (9).

Lysing reagents and fixatives were evaluated for their ability to inactivate HIV-infected H9 cells in whole blood preparations. All of the commercial lysing and fixing reagents inactivated cell-associated HIV by 3–5 log₁₀. Ammonium chloride had little effect (24).

Phenolic compounds at two to four times the manufacturer's recommended concentrations were shown to be effective in inactivating FCV on stainless steel surfaces (22).

Iodophor (ProMedyne-D) diluted to provide 75 ppm titratable iodine required three to 10 minutes of exposure on a hydrocolloid dental impression for inactivation of VSV (12).

As an alternative to glutaraldehyde, electrolyzed acid water (EAW) was evaluated as a disinfectant. DHBV infectivity was completely lost after incubation of the inoculum with 100 volumes of EAW for seven minutes or with 500 volumes for one minute (25).

Formaldehyde, β-propiolactone, and Virkon S (a peroxymonosulfate-based compound) were effective in inactivation of an astrovirus. The astrovirus, however, was resistant to heat inactivation, low pH, detergent, and phenolic, quaternary ammonium, or benzalkonium chloride-based products (26).

Disinfection in Plasma Products

Methods found in the literature for disinfection in the presence of plasma or plasma products include sodium hydroxide and heat, sodium hypochlorite and sodium dichloroisocyanurate, and others.

Sodium hydroxide and heat. Although not performed in the presence of plasma or plasma products, 0.1 M NaOH at 60°C was found to be an effective clean-in-place system for the inactivation of viruses present in plasma. Treatment of HAV with up to 1.0 M NaOH at 15°C did not lead to rapid inactivation. However, a two-minute contact time with 0.1 M NaOH at 60°C was sufficient to inactivate HAV, CPV, PRV, and BVDV (27). In another study, it was found that at 60°C, 0.25 M NaOH inactivated greater than 3.5 log₁₀ of CPV and HAV in 30 minutes, but inactivation was not complete (≤ 6 log₁₀) for either virus. For HAV, only 2.7 log₁₀ were inactivated after exposure to 0.1 M NaOH at 25°C for two hours. CPV was inactivated by more than 3.5 log₁₀, but inactivation was also incomplete. A two-hour exposure to 0.5 M NaOH at 4°C provided a reduction of more than 5 log₁₀ of CPV, but for HAV it was only a reduction of 2.4 log₁₀. Even for the CPV, inactivation was incomplete (21). The data for HAV inactivation from these two studies are summarized in Table 2.

Sodium hypochlorite (NaOCl) and sodium dichloroisocyanurate (NaDCC). A two-minute exposure of DHBV- and HBV-rich plasma to NaOCl (domestic bleach 3,600 ppm and industrial bleach 3,180 ppm) and NaDCC (3,000 ppm available chlorine) was sufficient for inactivation. Inactivation was found to be concentration dependent but independent of contact time. (28).

Other disinfectant studies. HBV-infected plasma was exposed to various disinfectants. Sodium hypochlorite at 1,000 ppm free chlorine provided only minimal inactivation, and povidone-iodine at 9, 5, and 3.6% provided no measurable inactivation. Sodium hypochlorite at 4,700 ppm free chlorine, 1% glutaraldehyde, and an iodophor-detergent disinfectant containing 3.6% povidone-iodine reduced viral titers by more than 3–4 log₁₀ (29).

A review of HIV inactivation by various disinfectants included information on plasma and various plasma products. The data are summarized in Table 1. The differences in inactivation for the FVIII concentrate seem to be related to the inoculum size. For the two test articles with 150-minute contact times, the inoculum was 4.5 log₁₀ TCID₅₀. For the two with 20–300 minutes of contact time, the inoculum was 6 log₁₀ TCID₅₀ per mL (23).

Culture Media

Cell-free HIV in RF-10 culture medium (10% fetal calf serum [FCS] in culture medium RPMI 1640) was inactivated within one minute by various disinfectants, as determined by CPE. The supernatants, however, contained p24 antigen levels in the samples treated with glutaraldehyde, potassium monopersulfate-based products, and ethanol. The final concentrations of the active ingredients in those disinfectants were 0.5% glutaraldehyde, 0.5% potassium monopersulfate, 2,500 ppm hypochlorite, 1:40 quaternary ammonium compounds, 0.8% iodine, 1:100 phenolics, and 35% ethanol. Cell-associated HIV was completely inactivated by glutaraldehyde, hypochlorite, iodine, phenolics, and 75% ethanol after a one-minute exposure. Cell-associated HIV was not completely inactivated by 35% ethanol, a potassium monopersulfate-based product, or quaternary ammonium product even after five minutes. Elevated p24 levels were found, without CPE, in glutaraldehyde, iodine, 75% ethanol, and phenolic compounds (9).

Data compiled in a review on the inactivation of HIV by disinfectants showed that one to two percent alkaline glutaraldehyde with a contact time of one to 10 minutes was sufficient to completely inactivate a spike of 3 log₁₀ of HIV into tissue culture fluid. Formaldehyde at a concentration up to 2% reduced a log₁₀ spike of 5.27 by more than 4.27 log₁₀ after five minutes. A 50% ethanol solution reduced HIV in tissue culture fluid by more than 3.52 log₁₀, and 35% isopropanol provided greater than 3.78 log₁₀ reduction. Povidone-iodine at a 1:40 solution and Betadine surgical scrub at a 1:60 dilution, both in the presence of 20% FCS, did not inactivate HIV. Quaternary ammonium compounds, however, inactivated more than 3 log₁₀ of HIV in the presence of 10% FCS after 10 minutes. Psoralen plus UV light (365 nm) did not inactivate HIV in tissue culture fluid after a four-minute exposure, but more than 6 log₁₀ were inactivated after two hours (23). UV light inactivation of HIV in culture medium is also discussed by Druce (9).

Benzalkonium chloride inactivated HIV-1 in 0.05% tissue culture fluid (30). The ability of sanitizing agents to inactivate human viruses in a 10% bovine serum albumin and yeast extract mixture was assessed. The sanitizing agents included a

benzalkonium chloride-based product, a chloroxylenol, cetrimide/chlorhexidine, and povidone-iodine. All of the products were effective in inactivating HSV and HIV-1, but a human coronavirus and human nonenveloped viruses (polio, ADV, and coxsackie virus) were not inactivated, with one exception. A benzalkonium chloride product (Dettol hospital concentrate) was able to inactivate the nonenveloped human coxsackie virus (31).

Bleach (5.25% sodium hypochlorite) at a 1:10 or 1:100 dilution was found to effectively inactivate RSV in up to 50% FCS (32).

HIV-1, HAV, RSV, vaccinia, HSV-1, and polio-2 were used to evaluate the capability of a hydrogen peroxide gas plasma sterilization process. The test viruses were suspended in cell culture medium and dried on the bottom of sterile glass petri dishes. This technique was effective against both lipid and nonlipid viruses. Viral titers were reduced from 2.5 log₁₀ to 5.5 log₁₀, a 99.68% to 99.999% decrease (33).

Making This Series Dynamic

This article series has presented published viral inactivation methods from the past decade and into 2001. Reviews that were published while preparing this series include one that addresses blood components (34), one that addresses plasma derivatives (35), and one prepared by the Council of Europe's Expert Committee in Blood Transfusion that addresses labile blood products (36). I am sure that many other valuable publications were missed because the literature search was limited to make it manageable. The reference list will be posted on the *BioPharm International* website (www.biopharm-mag.com), and we encourage readers to send us publication information that is not provided in the series (published articles dating from 1990 and beyond). You can email additional article references to associate editor Penny Cass at pcass@advanstar.com to help make the database a useful resource for all.

This review on virus inactivation was suggested by Dr. Jeri Ann Boose and

Dr. Michael Wiebe, and I would like to thank them for their encouragement. The final article in this series will discuss variability for specific viruses culled from a large database. **BPI**

References

- (1) Sofer, G., "Virus Inactivation in the 1990s — and into the 21st Century, Part 1: Skin, Bone, and Cells," *BioPharm* 15(7), 18–24 (July 2002).
- (2) Sofer, G., "Virus Inactivation in the 1990s — and into the 21st Century, Part 2: Red Blood Cells and Platelets," *BioPharm* 15(8), 42–49 (August 2002).
- (3) Sofer, G., "Virus Inactivation in the 1990s — and into the 21st Century, Part 3a: Plasma and Plasma Products (Heat and Solvent/Detergent Treatments)," *BioPharm* 15(9), 28–42 (September 2002).
- (4) Sofer, G., "Virus Inactivation in the 1990s — and into the 21st Century, Part 3b: Plasma and Plasma Products (Treatments Other than Heat or Solvent/Detergent)," *BioPharm* 15(10), 42–49, 51 (October 2002).
- (5) Sofer, G., "Virus Inactivation in the 1990s — and into the 21st Century, Part 4: Culture Media, Biotechnology Products, and Vaccines," *BioPharm Int.* 16(1), 50–57 (January 2003).
- (6) Reddish, G.F., *Antiseptics, Disinfectants, Fungicides and Chemical and Physical Sterilization* 2nd Ed. (Lea & Febiger, Philadelphia, 1957), pp. 23–29.
- (7) Nakagami, T. et al., "Inactivation of Herpes Viruses by High Hydrostatic Pressure," *J. Virol. Methods* 38(2), 255–261 (August 1992).
- (8) Neighbor, N.K. et al., "The Effect of Microaerosolized Hydrogen Peroxide on Bacterial and Viral Poultry Pathogens," *Poult. Sci.* 73(10), 1511–1516 (October 1994).
- (9) Druce, J.D. et al., "Susceptibility of HIV to Inactivation by Disinfectants and Ultraviolet Light," *J. Hosp. Infect.* 30(3), 167–180 (July 1995).
- (10) Ceisel, R.J. et al., "Evaluating Chemical Inactivation of Viral Agents in Handpiece Splatter," *J. Am. Dent. Assoc.* 126(2), 197–202 (February 1995).
- (11) Shapshak, P. et al., "Inactivation of Human Immunodeficiency Virus-1 at Short Time Intervals Using Undiluted Bleach," *J. Acquir. Immune. Defic. Syndr.* 6(2), letter, see comments, 218–219 (February 1993).
- (12) Look, J.O. et al., "Preliminary Results from Disinfection of Irreversible Hydrocolloid Impressions," *J. Prosthet. Dent.* 63(6), 701–707 (June 1990).
- (13) Farr, R.W. and Walton, C., "Inactivation of Human Immunodeficiency Virus by a Medical Waste Disposal Process Using Chlorine Dioxide," *Infect. Control. Hosp. Epidemiol.* 14(9), 527–529 (September 1993).
- (14) Modak, S. et al., "Rapid Inactivation of Infectious Pathogens by Chlorhexidine-Coated Gloves," *Infect. Control Hosp. Epidemiol.* 13(8), 463–471 (September 1993).

Continued on page 71

Virus Inactivation continued from page 48

- (15) Bailly, J.L. et al., "Activity of Glutaraldehyde at Low Concentrations (Less than 2%) Against Poliovirus and Its Relevance to Gastrointestinal Endoscope Disinfection Procedures," *Appl. Environ. Microbiol.* 57(4), 1156-1160 (April 1991).
- (16) Deva, A.K. et al., "Establishment of an In-Use Testing Method for Evaluating Disinfection of Surgical Instruments Using the Duck Hepatitis B Model," *Hosp. Infect.* 33(2), 119-130 (June 1996).
- (17) Chambon, M., Bailly, J.L., and Peigue-Lafeuille, H., "Comparative Sensitivity of the Echovirus Type 25 JV-4 Prototype Strain and Two Recent Isolates to Glutaraldehyde at Low Concentrations," *Appl. Environ. Microbiol.* 60(2), 387-392 (February 1994).
- (18) Van Bueren, J., Larkin, D.P., and Simpson, R.A., "Inactivation of Human Immunodeficiency Virus Type 1 by Alcohols," *J. Hosp. Infect.* 28(2), 137-148 (October 1994).
- (19) Sagripanti, J.L., Routson, L.B., and Lytle, C.D., "Virus Inactivation by Copper or Iron Ions Alone and in the Presence of Peroxide," *Appl. Environ. Microbiol.* 59(12), 4374-4376 (December 1993).
- (20) Shirai, J. et al., "Effects of Quaternary Ammonium Compounds with 0.1% Sodium Hydroxide on Swine Vesicular Disease Virus," *J. Vet. Med. Sci.* 59(5), 323-328 (1997).
- (21) Van Engelenburg, F., Over, J., and Hiemstra, H., "Evaluation and Development of Sanitization Conditions for Chromatography and Filtration Steps," paper presented at the PDA/FDA Viral Clearance Forum, Bethesda, MD, 1-3 October 2001.
- (22) Gulati, B.R. et al., "Efficacy of Commonly Used Disinfectants for the Inactivation of Calicivirus on Strawberry, Lettuce, and a Food-Contact Surface," *J. Food Prot.* 64(9), 1430-1434 (2001).
- (23) Sattar, S.A., "Springthorpe vs. Survival and Disinfectant Inactivation of the Human Immunodeficiency Virus: A Critical Review," *Rev. Infect. Dis.* 13(3), 430-447 (May-June 1991).
- (24) Nicholson, J.K. et al., "Inactivation of HIV-Infected H9 Cells in Whole Blood Preparations by Lysing/Fixing Reagents Used in Flow Cytometry," *J. Immunol. Methods* 160(2), 215-218 (2 April 1993).
- (25) Yamaguchi, T. et al., "Inactivation of a Hepadnavirus by Electrolysed Acid Water," *J. Antimicrob. Chemother.* 46(3), 363-368 (September 2000).
- (26) Schultz-Cherry, S., King, D.J., and Koci, M.D., "Inactivation of an Astrovirus Associated with Poultry Enteritis Mortality Syndrome," *Avian Diseases* 45, 76-82 (2001).
- (27) Borovec, S. et al., "Inactivation Kinetics of Model and Relevant Blood-Borne Viruses by Treatment with Sodium Hydroxide and Heat," *Biologicals* 26(3), 237-244 (September 1998).
- (28) Tsiquaye, K.N. and Barnard, J., "Chemical Disinfection of Duck Hepatitis B Virus: A Model for Inactivation of Infectivity of Hepatitis B Virus," *J. Antimicrob. Chemother.* 32(2), 313-323 (August 1993).
- (29) Payan, C. et al., "Inactivation of Hepatitis B Virus in Plasma by Hospital In-Use Chemical Disinfectants Assessed by a Modified HepG2 Cell Culture," *J. Hosp. Infect.* 47(4), 282-287 (2001).
- (30) Wainberg, M.A. et al., "Inactivation of Human Immunodeficiency Virus Type 1 in Tissue Culture Fluid and in Genital Secretions by the Spermicide Benzalkonium Chloride," *J. Clin. Microbiol.* 28(1), 156-158 (January 1990).
- (31) Wood, A. and Payne, D., "The Action of Three Antiseptics/Disinfectants Against Enveloped and Nonenveloped Viruses," *J. Hosp. Infect.* 38(4), 283-295 (April 1998).
- (32) Krilov, L.R. and Harkness, S.H., "Inactivation of Respiratory Syncytial Virus by Detergents and Disinfectants," *Pediatr. Infect. Dis. J.* 12(7), 582-584 (July 1993).
- (33) Roberts, C. and Antonoplos, P., "Inactivation of Human Immunodeficiency Virus Type 1, Hepatitis A Virus, Respiratory Syncytial Virus, Vaccinia Virus, Herpes Simplex Virus Type 1, and Poliovirus Type 2 by Hydrogen Peroxide Gas Plasma Sterilization," *Am. J. Infect. Control* 26(2), 94-101 (July 1993).
- (34) Corash, L., "Inactivation of Infectious Pathogens in Labile Blood Components: Meeting the Challenge," *Transfus. Clin. Biol.* 8, 138-145 (2001).
- (35) Morgenthaler, J.J., "Securing Viral Safety for Plasma Derivatives," *Transfus. Med. Rev.* 15(3), 224-233 (2001).
- (36) Council of Europe, "Pathogen Inactivation of Labile Blood Products," *Transfus. Med.* 11, 149-175 (2001).

BioPharm International (ISSN 1542-166X) is published monthly by Advanstar Communications, Inc., 131 W. First Street, Duluth, MN 55802-2065. **Subscription rates:** \$64 for one year in the United States and Possessions; \$84 for one year in Canada and Mexico; all other countries \$124 for one year. Single copies (prepaid only): \$7 in the United States; \$9 all other countries. Back issues, if available: \$19 in the United States, \$23 all other countries. Add \$5 per order for shipping and handling. **Periodicals postage paid** at Duluth, MN 55806, and additional mailing offices. **POSTMASTER:** Please send address changes to *BioPharm International*, PO Box 6128, Duluth, MN 55806-6128, USA. Canadian GST number: R-124213133RT001, Publications Mail Agreement Number 40017597. Printed in U.S.A. **Right to privacy:** Advanstar Communications, Inc., provides certain customer contact data (such as customers' names, addresses, phone numbers, and email addresses) to third parties who wish to promote relevant products, services, and other opportunities that may be of interest to you. If you do not want Advanstar Communications to make your contact information available to third parties for marketing purposes, simply call toll-free 888.527.7008 between the hours of 7:30 AM and 5 PM and follow the instructions to remove your name from Advanstar's lists.

©2003 Advanstar Communications, Inc. All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including by photocopy, recording, or information storage and retrieval system, without permission in writing from the publisher. Authorization to photocopy items for internal or personal use or the internal or personal use of specific clients is granted by Advanstar Communications, Inc., for libraries and other users registered with the Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01923, 978.750.8400, fax 978.750.4470; call for copying beyond that permitted by Sections 107 or 108 of the U.S. Copyright Law. For those not registered with the CCC, send permission request in writing to Permissions Department, Advanstar Communications, Inc., 7500 Old Oak Boulevard, Cleveland, OH 44130, or fax to 440.891.2740. *BioPharm International* does not verify any claims or other information appearing in any of the advertisements contained in the publication, and cannot take any responsibility for any losses or other damages incurred by readers in reliance on such content.

