Readers' Forum

FDA Labeling Requirements for Disinfection of Endoscopes: A Counterpoint

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ABSTRACT

Endoscopes are used widely for the diagnosis and therapy of medical disorders. To prevent spread of nosocomial infection, all endoscopes should undergo thorough cleaning and high-level disinfection following each use. The Food and Drug Administration (FDA) has approved a user-friendly package label for one liquid chemical germicide that requires a 45-minute immersion at 25°C to support a high-level disinfection label claim. Scientific data reviewed here suggest that one can achieve at least an 8-log reduction in *M tuberculosis* contamination with cleaning (4 logs) followed by chemical disinfection for 20 minutes (4 to 6 logs). The FDA should modify the label to state that if cleaning is accomplished using a standardized cleaning protocol, then a 20-minute immersion at 20°C will be sufficient to achieve high-level disinfection. *(Infect Control Hosp Epidemiol* 1995;16:231-235).

Endoscopes have been used widely for the diagnosis and therapy of medical disorders and are used increasingly for performing laparoscopic surgery. Endoscopes are contaminated routinely by microorganisms during clinical use. Failure to employ appropriate disinfection or sterilization of endoscopes has been responsible for multiple nosocomial outbreaks.[1,2] To prevent the spread of nosocomial infection, all endoscopes should be cleaned and disinfected thoroughly according to current guidelines after every patient use.[3-5]

The increasing incidence of tuberculosis and increased numbers of immunocompromised patients have focused attention on the need for disinfection of semicritical items (items such as endoscopes that touch mucous membranes) to eliminate *Mycobacterium tuberculosis.* Because mycobacteria are the most resistant group of microorganisms (with the exception of bacterial endospores), inactivation of mycobacteria serves to demonstrate the inactivation of all pathogenic vegetative organisms including viruses (eg, HIV, HBV, polio), bacteria (eg, *Pseudomonas aeruginosa, Staphylococcus aureus*), and fungi (eg, *Candida, Trichophyton*).

In June 1993, a memorandum of understanding (MOU) was signed by the Environmental Protection Agency (EPA) and the Food and Drug Administration (FDA) regarding the regulation of liquid chemical germicides.[6] Liquid chemical germicides are classified both as "pesticides" under the EPA's Federal Insecticide, Fungicide, and Rodenticide Act and as "devices" under the FDA's Food, Drug, and Cosmetic (FD&C) Act. Historically, the EPA has regulated the efficacy of liquid chemical germicides. For nearly 30 years, the EPA or its predecessor (the Pesticide Program Branch of the US Department of Agriculture) performed intramural preregistration and postregistration efficacy testing of some chemical disinfectants. In 1982, this practice was stopped, reportedly for budgetary reasons. In 1992, the EPA resumed verification testing of manufacturers' sporicidal activity claims. The MOU separated liquid chemical germicides into two categories: sterilants and general purpose disinfectants. EPA was given primary jurisdiction to regulate general purpose disinfectants used on noncritical items (items that come into contact with intact skin, such as floors and countertops). All sterilants used to reprocess critical (devices that enter sterile tissue or the vascular system, such as surgical instruments) and semicritical devices were

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TABLE 1
EFFECTIVENESS OF CLEANING IN ELIMINATING MICROBIAL CONTAMINATION OF ENDOSCOPES

Investigator	Endoscope	Pathogen*	Initial Contamination (log_{10})	Post-Cleaning Contamination (log_{10})	Mean Log Decrease	Time to Sterility Using 2% Glutaraldehyde
Hanson, 1989[10]	Gastrointestinal	Mixed bacteria	3.0-4.6 cfu/mL	0†	4.9	<2 min
	Olympus GIFXQ20	HIV, HBV	ND	0		
Hanson, 1990[11]	Gastrointestinal Olympus GIFXQ20‡	HIV	4.7-6.5 pg/mL	0-2.2§	4.7	<2 min
Hanson, 1991[12]	Bronchoscope	Mixed bacteria	2.1-4.3 cfu/mL	0	2.8	<2 min
	Olympus BF10	*Pneumocystis carinii*	1.2 cysts/mL	0		
		HBV, HIV	ND	0		
Vesley, 1992[14]	Gastrointestinal Olympus CF-P10S‡ Olympus ERCP/JF10‡	*Bacillus subtilis*	6.0-8.0 cfu/mL	ND	4.2	ND
Hanson, 1992[13]	Bronchoscope Olympus BF10‡	*M tuberculosis*	3.1-4.6 cfu/mL	0.11-0.7	3.5	<10 min

*HIV = human immunodeficiency virus, HBV = hepatitis B virus.
†Removed all organisms from 66/68 contaminated sites; *Neisseria* species recovered from two channels.
‡Experimental contamination.
§HIV antigen was undetectable on 4 endoscopes and reduced to 165 pg/mL on the fifth.
ND = no data, cfu/mL = colony forming units/mL.

regulated as "devices" by the FDA. Chemical sterilants that are used to kill all microorganisms (with the exception of high numbers of bacterial spores) in short exposure times (<30 minutes) are called high-level disinfectants.

Because liquid chemical sterilants regulated by the FDA are considered medical "devices," the manufacturer must receive a written 510(k) clearance to market the product legally. A 510(k) clearance (literally section 510[k] of the FD&C Act) is the premarket notification of a medical device or accessory to a medical device. The data required by the FDA are quite rigorous.[7]

In April 1994, Johnson & Johnson Medical Inc. received the first written 510(k) clearance from the FDA for their glutaraldehyde-based disinfectant/sterilant healthcare products (ie, Cidex solutions). In September 1994, Johnson & Johnson implemented the required 510(k) clearance changes by altering the package label and including a package insert.[8] The time and temperature specified for Cidex-activated dialdehyde (2.4% glutaraldehyde) solution was 45 minutes at 25°C (77°F) to support a high-level disinfection claim (ie, 100% kill of *M tuberculosis*). Although Cidex has had this label claim since 1984, the FDA has required the manufacturer to alter its package insert to state precisely that immersion for 45 minutes at 25°C is required for high-level disinfection. It is thought that similar competitive 2% alkaline glutaraldehyde products will have comparable label claims.

These new FDA label claims will necessitate substantial changes in infection control practices. A 1989 survey revealed that 44% of hospitals in one state immersed endoscopes in a high-level disinfectant for less than or equal to 10 minutes.[9] Current guidelines suggest 20 minutes or longer at 20°C is adequate to inactivate mycobacteria and all other vegetative pathogens reliably with high-level disinfectants.[3,4] The purpose of this Readers' Forum is to assess the scientific validity of requiring extended immersion times of 45 minutes at higher temperatures (25°C) for label claims of mycobacterial inactivation when using a 2% glutaraldehyde.

The process required by the FDA for a tuberculocidal label claim is very rigorous, because it uses a quantitative tuberculocidal test and requires 100% kill of *M tuberculosis*. Because the quantitative test does not allow for cleaning, is conducted in the presence of 2% horse serum (ie, a protein load), and uses an extremely high number of organisms (100,000 [5 logs] to 1,000,000 [6 logs]), an extended immersion time (eg, 45 minutes) and elevated temperature (25°C) are necessary to inactivate 100% of the mycobacteria. However, several investigators have shown that cleaning endoscopic equipment is extremely effective in eliminating microbial contaminants. These studies

TABLE 2
ACTIVITY OF GLUTARALDEHYDE SOLUTIONS AT 20°C AGAINST *MYCOBACTERIUM TUBERCULOSIS*

Investigator	Methodology	Type of Glutaraldehyde	Inoculum* (log_{10})	Log_{10} Reduction at Specified Time	Time to Sterility
Collins, 1986[15]	Suspension	2% alkaline	6.1	2.4 at 10 min	25 min estimated
Collins, 1986[16]	Suspension	2% alkaline	~4.0	~4.0 at <20 min	<20 min
	Carrier	2% alkaline	~4.7	~4.7 at 20 min†	ND
Collins, 1987[17]	Membrane filter	2% alkaline	~6.0	~6.0 at <15 min	<15 min
Ascenzi, 1987[18]	Suspension	2% alkaline	5.0‡	4.2 at 20 min	ND
Best, 1990[19]	Suspension	2% alkaline	ND	3.7 at 10 min	<30 min
	Carrier	2% alkaline	ND	3.4 at 10 min	<30 min
Cole, 1990[20]	Carrier	2% alkaline (Manufacturer #1)	6.1	6.1 at 20 min	<20 min
		2% alkaline (Manufacturer #2)	6.1	6.1 at 20 min	<20 min
Rutala, 1991[21]	Carrier	2% alkaline	6.4	6.4 at 20 min	<20 min
		2% acid	6.4	6.4 at 20 min	<20 min
Best, 1994[22]	Carrier	2% alkaline	ND§	>5.0 at 10 min>	<10 min

*Inoculum is expressed as organisms/mL for suspension tests and organisms/carrier for carrier tests.
†100% kill on 3/4 penicylinders in 20 min.
‡BCG strain.
§Multidrug-resistant *M tuberculosis* strain resistant to isoniazid, rifampin, streptomycin, and ethambutol.

(Table 1) have shown a mean 4.0 log reduction (99.99%) in the microbial contaminants with cleaning alone.[10-14] Cleaning is a very effective adjuvant because it removes pathogenic microorganisms on inanimate objects, as well as organic matter that may interfere with the microbiocidal activity of the germicide. Thus, cleaning allows the use of shorter exposure times to achieve high-level disinfection.

Cleaning is an essential step in preventing the indirect transmission of pathogens by medical devices. It should be done promptly following each use of an endoscope to prevent drying of secretions, allow removal of organic material, and decrease the number of microbial pathogens. However, the FDA may have chosen a standard that ignores cleaning because neither the FDA nor the manufacturer has control over the cleaning technique employed. Hence, a specific label statement cannot be made with regard to the potential decrease in immersion time achieved by cleaning. In the absence of cleaning and the presence of high microbial loads, immersion in a 2.4% alkaline glutaraldehyde for 45 minutes at 25°C may be necessary for 100% tuberculocidal kill. This statement should not be interpreted to mean that this is the preferred approach, or that prolonged immersion time is an adequate substitute for proper cleaning prior to high-level disinfection or sterilization. The Association for Professionals in Infection Control and Epidemiology, Inc, (APIC) recommendation of 20 minutes or longer at 20°C for high-level disinfection presumes precleaning with an enzymatic detergent or a detergent that removes debris and significantly reduces microbial contaminants. A survey has revealed that hospitals follow proper cleaning procedures.[9]

Two percent glutaraldehyde is an extremely effective disinfectant against a wide range of microorganisms, including *M tuberculosis*. Several investigators (Table 2) have demonstrated that glutaraldehyde solutions inactivate 2.4 to >5.0 logs of *M tuberculosis* in 10 minutes (including multidrug-resistant *M tuberculosis*) and 4.0 to 6.4 logs of *M tuberculosis* at 20 minutes.[15-22] Concern has been raised because a single investigator using the quantitative suspension test reported that 2% glutaraldehyde inactivated only 2 to 3 logs of *M tuberculosis* in 20 min at 20°C.[18] However, all other investigators[15-17,19-22] using various test methodologies, including a quantitative suspension test, have found much greater levels of *M tuberculosis* inactivation using 2% glutaraldehyde (Table 2).

In order to determine the overall efficacy of the standard disinfection procedures employed for reprocessing endoscopes, one must consider the consecutive reductions achieved with cleaning followed by disinfection. Scientific data suggest that one can anticipate at least an 8-log reduction in *M tuberculosis* contamination with cleaning (4 logs), followed by chemical disinfection for 20 minutes (4 to 6 logs). The maximum level of *M tuberculosis* contamination of an endoscope following clinical use has not been deter-

mined precisely. One investigator obtained quantitative cultures for multiple microorganisms, including viruses, bacteria, fungi, and protozoa from 10 bronchoscopes and 20 gastrointestinal endoscopes used on patients with AIDS. It was found that the level of contamination of any single organism never exceeded 8 logs (means, 1.18 to 4.34 log cfu/mL for each organism present).[10,12]

Some concerns that would make the new FDA labeling requirement justifiable include: failure to clean devices prior to disinfection; outbreaks of infection while following current disinfection guidelines; or ineffective concentrations of glutaraldehyde because dilution during use was not properly monitored. We believe these concerns are not supported by the scientific data. First, cleaning is practiced routinely in hospitals prior to disinfection, as confirmed by a study that surveyed approximately 100 hospitals.[9] Second, there have been no published reports of cross-transmission of pathogens when current guidelines[3] have been followed. Third, recommended monitoring of glutaraldehyde concentrations should eliminate the possibility of ineffective levels being used for high-level disinfection. A recent study found a glutaraldehyde concentration of 1.0% to 1.1% in manual and automatic baths used for endoscopes at the end of the 14-day reuse period.[23] Most studies suggest that 1.0% glutaraldehyde is the minimum effective concentration when used as a high-level disinfectant,[20,24,25] although one investigator using atypical mycobacteria showed the minimum effective concentration should be 1.5%.[23] Currently available glutaraldehyde test strips are constructed to indicate concentrations above 1.5%. Therefore, to ensure that the appropriate concentration of glutaraldehyde is present, the solution should be monitored periodically, with the exact frequency based on how often the solutions are used (eg, if used daily, test daily). Testing should not be used to extend the use-life beyond the expiration date.

The failure to consider the effectiveness of cleaning invalidates the use of FDA-required label claims to determine the duration of exposure to 2% glutaraldehyde when used to achieve disinfection in clinical practice. It is inconsistent for the label on the Cidex bottle to specify that cleaning is a prerequisite to disinfection, but not to include the efficacy of cleaning in developing a label claim. For example, Hanson et al examined 30 endoscopes used on persons with AIDS and found that cleaning alone removed all detectable contamination from 84 of 86 contaminated sites.[26] Cleaning removed HIV to such an extent that virus was undetectable even by a polymerase chain reaction (PCR), a process that can identify one infected cell in a background of 10^6 uninfected cells.

The FDA should be commended for approving a user-friendly package label and insert that more precisely identify how to achieve high-level disinfection. We agree with the package insert, which states that medical devices must be thoroughly cleaned, rinsed, and rough dried before immersion in an activated glutaraldehyde. We believe that the FDA should modify the package insert to state that if cleaning is accomplished using a standardized cleaning protocol, then a 20-minute immersion at 20°C will be sufficient to achieve high-level disinfection. If cleaning did not occur (which is not an acceptable practice), then high-level disinfection should be accomplished with an exposure time of 45 minutes at 25°C.

Extending the exposure of endoscopes to chemical sterilants will increase the cost of all endoscopic procedures by slowing reprocessing time and, hence, requiring the purchase of additional devices. Another consequence of prolonged immersion of endoscopes could be moisture damage or corrosion, resulting in shorter use-life of the endoscopes. We believe that adherence to the current APIC recommendation of precleaning, followed by a 20-minute or longer immersion in a 2% glutaraldehyde at 20°C for high-level disinfection, provides a substantial margin of safety in preventing person-to-person transmission of *M tuberculosis* or other pathogens. This position is supported both by the scientific literature summarized in this paper and by the absence of cases of person-to-person transmission of *M tuberculosis* when the current APIC guidelines[3] were used.

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