



OCCASIONAL SURVEY

International Society for Cell Therapy Facility Sanitization Survey Laboratory Practices Committee Report

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Abstract

Background aims. Quality cell manufacturing processes require a clean laboratory environment. **Methods.** This report was aimed at describing current cleaning and sanitization practices reported by facilities that manufacture many types of cellular therapy products for clinical use. It is our hope that this report may provide the groundwork for guidance recommendations directed at developing consensus standards for cleaning and sanitization practices across the globe. Facility sanitization is a central issue to regulatory and accreditation bodies. Facilities are required to develop plans to assess sanitization practices and test cleaning effectiveness. **Results.** This document provides information on how this is performed in different facilities and may allow newer, smaller or less developed facilities to build, enhance or revise their current quality program by using experience and expertise in facility sanitization reported herein. **Conclusions.** This report summarizes the results of the latest survey and compares results with those previously reported. New and relevant trends in the field provide important information and will provide important information for establishing guidelines.

Key Words: *classification, processing facilities, regulation, sanitization*

Introduction

Maintaining a clean laboratory is an essential element of a high-quality cell manufacturing process. It is imperative to attain and maintain an extremely low number of particles of any kind, organic and inorganic, as well as the absence of microorganisms, and to demonstrate control of a clean environment. Good Manufacturing Practices (GMPs) and Good Tissue Practices (GTPs) require that any facility that processes cellular therapy products must be maintained in a clean and orderly fashion. These requirements are spelled out in the Code of Federal Regulations parts 211, 600, 820, 1271 [1] in the United States and European Commission Directive 2006/86/EC and EU Guidelines to Good Manufacturing Practice, Annex 1 01 March 2009 in the European Union [2]. Health Canada, the Therapeutic Goods Administration in Australia and other

competent authorities around the world have similar requirements. The Foundation for the Accreditation of Cellular Therapy (FACT) standard D.2.4 [3] also requires the cellular processing facility to be maintained in a clean, sanitary and orderly manner. This includes all equipment used during the manufacture of cellular therapy products as well as facility itself.

In September 2003, the International Society for Cell Therapy (ISCT) announced the formation of a working group to address facility sanitization in cellular therapy processing facilities. The ISCT Laboratory Practices Committee (LPC) organized and continues to sponsor this group. A mission statement was identified to determine the focus of the project. The LPC Working Group planned to draft a document to include regulatory guidance and outline practices regarding appropriate facilities/equipment cleaning and sanitization involved in the

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manufacture and processing of cellular therapy products. Input was sought from experts in the cell therapy community and pharmaceutical industries, regulatory agencies and other interested stakeholders. The Working Group agreed that a survey to collect the cleaning practices of the industry was warranted, and such a survey was developed and disseminated through the use of a web-based survey tool to the membership of ISCT, AABB and American Association of Tissue Banks in early 2005. There were 55 respondents. Because no guidance document or white paper was forthcoming and facilities have changed over time, a follow-up survey was created by the LPC in 2010 to gain a more current perspective on how facilities have modified their practices regarding approaches to facility sanitization. One hundred eight facilities (132 laboratories) responded to this new survey. Several of the same questions from the previous version were included, and additional questions were added, requesting more detail on certain topics to describe current industry practices. This report focuses on the results of 2010 survey.

There are very few and very limited descriptions of these procedures and practices; therefore, the goal in creating this document is to describe current cleaning and sanitization practices reported by facilities that manufacture all types of cellular therapy products for clinical use. This first step will provide the groundwork for guidance recommendations directed at developing consensus standards for cleaning and sanitization practices across the globe. Facility sanitization is becoming more important to regulatory and accreditation bodies, and facilities must develop plans to assess sanitization practices and test cleaning effectiveness. Maintaining a clean laboratory is a key element of a quality manufacturing process. In effect, this document may allow newer, smaller or less developed facilities to build, enhance or revise their current quality program by using the vast experience and expertise in facility sanitization reported herein. This report summarizes the results of the latest survey and compares the relevant trends in the field that provide important information for guidance with those previously reported. Ultimately, each facility should conduct its own risk-based assessments and validations regarding which practices are indicated, acceptable or feasible within that facility.

Methods

There are several terms that require definition in the context of this survey. “Sanitization” is defined as cleaning the surface to kill microorganisms that may be present. “General cleaning” is defined as cleaning of the facility and/or equipment that is regularly

Table I. Survey composition by section and the number of questions asked in each section.

Survey section	No. of questions
General demographics, laboratory type, regulatory, quality standards, misc	14
General laboratory cleaning and reagents	8
Extensive laboratory cleaning, cleaning staff, training and supplies	10
BSCs	9
Equipment cleaning	12
Manufacturing lab accessories, clothing, personal protective equipment	12
Environmental monitoring	12

performed before and/or at the completion of processing as defined by each facility. “Extensive cleaning” can be thought of as “spring cleaning” and involves less frequent periodic heavy-duty cleaning and sanitization of walls, ceilings and other components. “General cleaning” of the biological safety cabinet, for example, may involve disinfecting and wiping it down before and/or after each use. Extensive cleaning may involve disassembling of the biological safety cabinets (BSC) and performing a more thorough deep cleaning and sanitization of each individual part. “Mopping” is defined as floor cleaning by means of a mop, soap and water or a mop handle and disposable sanitizing/cleaning pads.

The current survey questions were compiled in a fashion similar to the previous survey of 2005 by the members of the LPC under the leadership of Andrew Havens. The survey was submitted to memberships of ISCT, AABB and American Association of Tissue Banks. There were 108 respondent facilities (132 laboratories) in this survey compared with 55 respondents in the 2005 survey. The international distribution of the participants was 67% United States, 14% Canada, 12% Europe, 5% Australia/New Zealand and 2% Israel. The composition of the survey questions is described in [Table I](#).

Results

Types of laboratories by air classification, products handled and regulatory status of products

In the current survey, 63 of 132 respondent laboratories (47%) reported having a standard laboratory (unclassified air); 43% have some form of classified/certified lab space ([Figure 1A](#)). In the 2005 survey, 49% reported the use of unclassified laboratory facilities, with 48% having some air classification. In this survey, a similar proportion of laboratories processing cellular products use standard (unclassified) laboratories. These results point to stability in the relative number of laboratories that use unclassified air conditions.

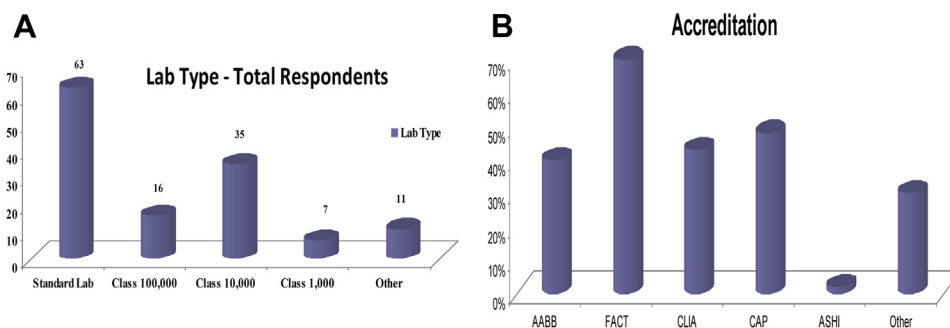


Figure 1. (A) Laboratory classification types. (B) Facility accreditation. (A) Number and percent of laboratories that use different types of air classification are shown. The percentage of respondents is indicated on the y-axis; the number of total responding laboratories appears at the top of each bar. Some of the responders have more than one type of air classification. (B) Percentage of laboratories reporting registration by the various accreditation programs.

The majority of hematopoietic progenitor cells, apheresis (HPC-A) and hematopoietic progenitor cells, marrow (HPC-M) products were processed in unclassified laboratories, whereas 25% of more-than-minimally manipulated products were processed under these conditions. Cord blood products in general appear to benefit from more stringent conditions because of the regulatory requirements of processing these units. Hematopoietic progenitor cells, cord blood (HPC-C) bankers processed 35% of their products under class 10,000 or 1000 conditions. Although this survey encompasses more than double the number of sites than the previous survey several years ago, the relative proportion (percentage) of investigational new drug (IND) products or products used in phases I, II and III are very similar. The types of products processed under the various laboratory conditions are summarized in Table II. In the current study, 75% of the respondents reported that they process minimally manipulated “standard of care” cellular products (Table II). The regulatory status of cell therapy products is summarized in Supplementary Table 1S: 41% of the respondents reported processing/manufacturing cells under IND, and 34% do so for some phase of clinical trials (Supplementary Table 1S).

Regulatory status of laboratories and inspections

A reported 84% of the facilities are registered with the US Food and Drug Administration (FDA), Therapeutic Goods Administration (TGA) or European Union (EU) regulatory bodies. Accreditation programs implemented in the various laboratories are presented in Figure 1B. The number of laboratories that have achieved FACT accreditation has increased from 47% to 70% since the last survey. Clinical Laboratory Improvement Amendments (CLIA) was included in a heterogeneous group (other) in the 2005 survey, whereas 43% of the responding laboratories are now CLIA-accredited. Accreditations from other standards setting organizations including AABB (40%), College of American Pathologists (CAP) (48%) for laboratory proficiency testing and American Society for Histocompatibility and Immunogenetics (ASHI) (2%) for histocompatibility testing did not differ from the last survey.

Quality assurance programs and inspections

Almost all (99%) of the facilities had a written quality assurance (QA) program. More than 90% of the unclassified laboratories have written Standard Operating

Table II. Type of cellular products produced under the various laboratory classifications.

Laboratory type products	Standard laboratory	Class 100,000 (>ISO 8)	Class 10,000 (ISO 7)	<Class 1000 (ISO 6)
HPC-A, HPC-M	57 66%	9 10%	14 16%	6 7%
HPC-C (banking)	12 41%	7 24%	6 21%	4 14%
HPC-C (thaw/wash/dilute for infusion)	32 57%	9 16%	11 20%	4 7%
Standard blood bank products	9 64%	3 21%	1 7%	1 7%
More-than-minimally manipulated/products manufactured under IND/other starting products	13 25%	7 13%	29 55%	4 8%

Top number indicates number of respondents selecting the option; bottom number, percentage of the product type in each environmental classification. A, apheresis; C, cord blood; M, bone marrow.

Table III. Commonly used disinfectants.

Cleaning agent	Action	Use
LPH disinfectant cleaner	A non-alkaline phenol Disinfectant	Broad-spectrum anti-microbial Has antiseptic properties, may not kill spores
70% alcohol	Germicidal properties	Effective against spores in addition to bacteria and viruses
10% bleach	A germicidal detergent	Broad-spectrum anti-microbial
VespheneIIse	A germicidal detergent	Broad-spectrum anti-microbial
Germicidal wipes	A surface disinfectant	Effective against viruses and bacteria and fungi
Cavicide	A ready-to-use sterilant	Effective against spores in addition to bacteria and viruses
Sporclenz	A quaternary formula	Kills a broad spectrum of bacteria and viruses
Virex		

Procedures (SOPs) that describe cleaning activities as well as cleaning documentation. In the previous survey, 70% of the facilities had written SOPs and records pertaining to cleaning. Source material for composing SOPs for cleaning and sanitization varied. Only 24% indicated that they follow a published standard for facility cleaning, emphasizing the need for written guidance documents. The laboratories that follow published standards for cleaning and sanitization most frequently reference International Organization for Standardization (ISO) 14644–5: Clean rooms and Associated Controlled Environments.

Our survey demonstrated that the governing regulatory body had inspected 53% of the facilities. The context in which inspections were performed were routine inspections (not for cause) (79%), with additional inspections performed under IND (22%), investigational device exemption (IDE) (3%), drug device master (7%) or other (3%).

Cleaning agents and testing cleaning effectiveness and/or process

The survey polled respondents regarding the specific cleaning agents they use and specific cleaning

methods and frequency. There are many disinfectant products from which to choose, and many different combinations were reported. A large number of facilities reported the use of similar items on a consistent basis, and a description of these agents is summarized in Table III. Seventy-seven of the laboratories reported the use of combinations of two and three different kinds of disinfecting agents. The most commonly used disinfectants were LpH, Vesphene or other phenolic-based compounds (Figure 2A). Alcohol 70%, isopropanol and bleach were also commonly used. Testing the effectiveness of cleaning procedures was reported in 52% of all total laboratories surveyed. An increase of 31% was reported in the number of unclassified laboratories that test the effectiveness of their cleaning procedure (41% compared with 10% in the previous report). Classified laboratory spaces (ISO 7–8) trended higher (Figure 2B). Microbial assessment/environmental monitoring of surfaces before and after cleaning was found to be the most common practice, with a small number of laboratories performing microbial challenge. Rotation of reagents was lower (25%) in standard unclassified laboratories than in the classified air facilities.

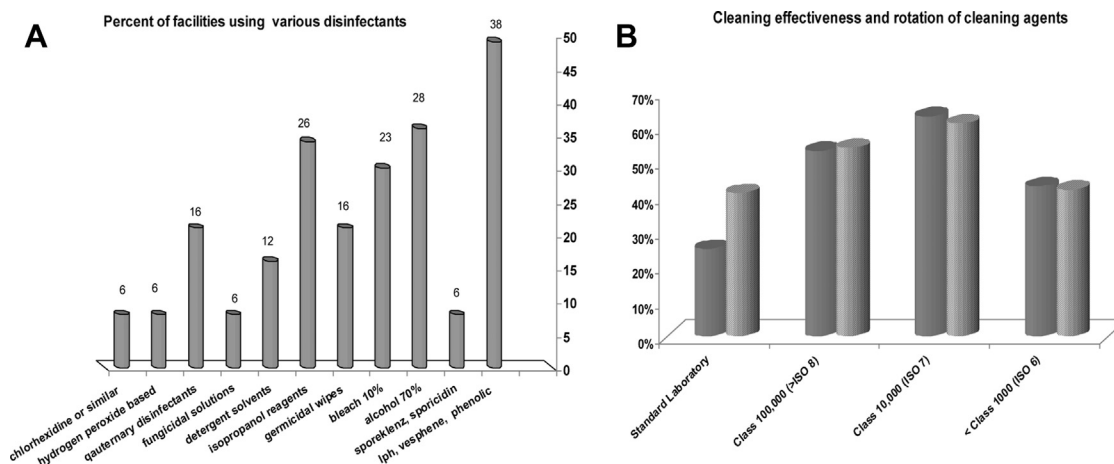


Figure 2. (A) Disinfecting agents used. (B) Cleaning effectiveness. (A) Percentages of laboratories that use each kind of disinfectant is indicated by the bar height (y-axis); the number of respondent labs appears above each bar. More than one choice was allowed, and most laboratories use a combination of two to three agents. (B) Measurement of testing cleaning effectiveness and rotating reagents. Hatched bars represent the percentage of responders who measured cleaning effectiveness; gray bars display the percentage of laboratories that rotate cleaning agents. Most of the classified laboratories perform both.

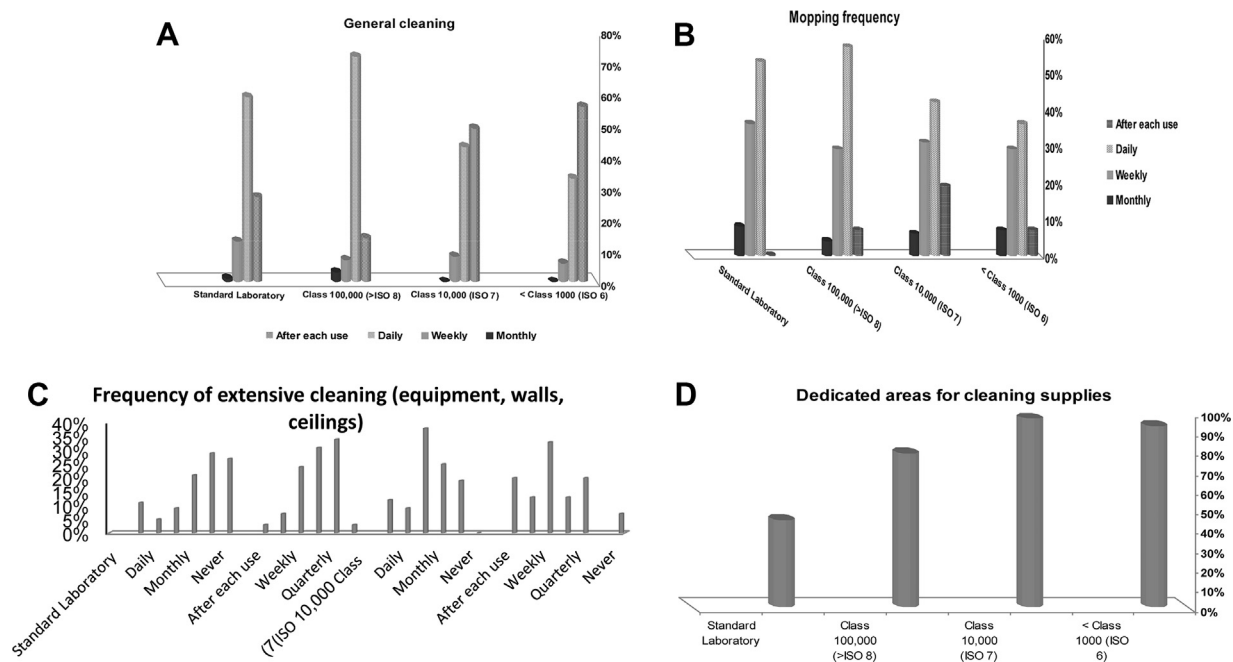


Figure 3. (A) Frequency of general cleaning by (B) floor mopping frequency, laboratory classification. (A) Proportion of different laboratory types cleaning intervals. The majority of standard and ISO 8 laboratories clean daily. Some of the sites had more than one laboratory type. (B) Proportion of different laboratory types and mopping intervals. Most laboratories reported mopping daily or weekly with some of the higher classified labs mopping after each use. (C) Presented are the different laboratory types of extensive cleaning intervals. Laboratories were asked the frequency of extensive cleaning including equipment, walls, ceilings and so forth. The time interval most often used in non-classified and ISO 8 labs was quarterly, whereas ISO 7 and ISO 6 more commonly cleaned weekly. (D) Presented is the percentage of type of facility with specifically dedicated areas for cleaning supplies and associated equipment. More than 90% of the classified and approximately half of the unclassified facilities have dedicated areas for cleaning supplies.

Cleaning and sanitization schedules

Standard laboratories and class 100,000 facilities cleaned once a day, with a minority of facilities cleaning after each procedure. More than half of the facilities with stricter air classification (ISO 7 or ISO 6) cleaned after every procedure. Most laboratories reported cleaning at least once daily (Figure 3A). Floor mopping, which may be part of general cleaning at many sites, was surveyed separately, and it was reported to be performed daily in more than 50% of the standard and ISO 8 laboratories and weekly in approximately 30% of all laboratories. Some of the higher-classified laboratories also report floor mopping after each procedure (Figure 3B).

Responses to the frequency of extensive cleaning, which included walls, ceilings and equipment, revealed that 25% to 40% of the laboratories perform this type of sanitization either weekly or monthly. Standard laboratories reported extensive cleaning monthly (21%), quarterly (29%) or never (27%), whereas a higher frequency was reported in the classified laboratories. ISO 8 labs reported extensive cleaning at a rate of 24% weekly, 31% monthly and 34% quarterly. Even more frequent extensive cleaning was reported from the ISO 7 and ISO 6 labs (38% reported carrying it out weekly) (Figure 3C). Areas dedicated for storage of cleaning

supplies were reported in 45% of the standard laboratories (unclassified) compared with 20% in the previous survey, providing a greater-than 100% increase. The majority of classified laboratories provide dedicated areas, and the ISO 7 and ISO 6 laboratories improved from 75% in the previous survey to greater than 90% (Figure 3D).

Frequency of heating, ventilation and air conditioning ventilation cleaning

The majority of laboratories (70%) clean their heating, ventilation and air conditioning (HVAC) systems at least once a year. The standard laboratories (unclassified) most often reported cleaning them annually, whereas the classified laboratories the HVAC vents were cleaned more often (Supplementary Table 2S).

Documentation of laboratory cleaning procedures

There has been an increase in the requirement for documentation of cleaning procedures in standard laboratories (unclassified) in comparison to the last survey. The current data reported cleaning activities in 90% of standard laboratories (unclassified), compared with 70% in 2005.

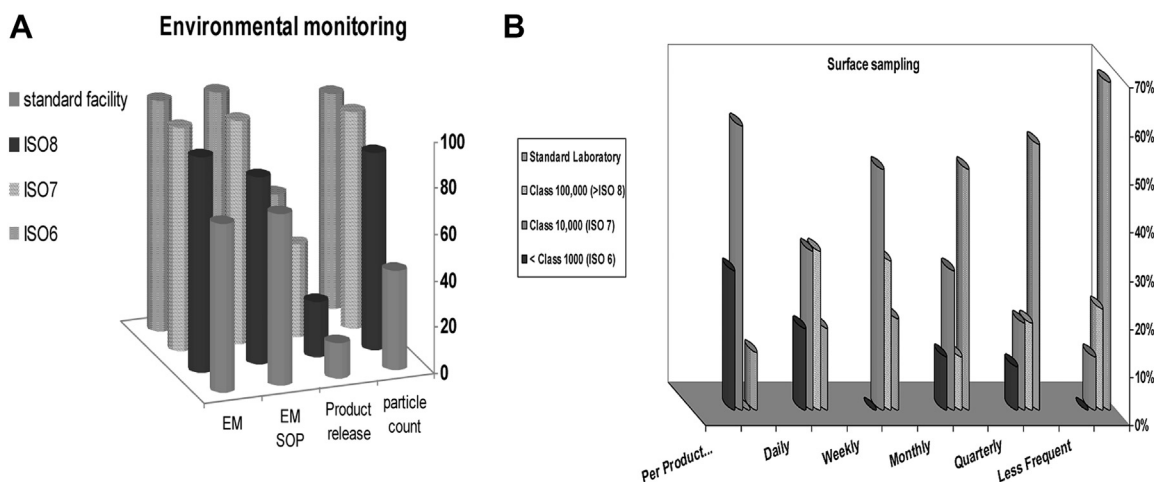


Figure 4. (A) Environmental monitoring. (B) Surface sampling frequency. (A) Percentage of laboratories of different types (Standard/unclassified, ISO 8, ISO 7 and ISO 6) who reported performing some aspects of environmental monitoring are presented. EM indicates that the facility performs environmental monitoring; EM SOP, the facility has an EM SOP. The results of EM are tied to product release; particle count indicates that particle count is performed. (B) EM time intervals used by different types of laboratories. Most of the standard laboratories monitored surfaces at least monthly.

Biological safety cabinets

More than 90% of the laboratories in this survey reported the use of class 100 BSCs, all certified at least once annually, and have written SOPs for cleaning these cabinets [4,5]. Cabinets were cleaned either after each use, after a spill or daily. Extensive cleaning of BSCs was routinely performed monthly, quarterly, biannually or annually by all laboratories, with no clear frequency in any group. Other types of extensive cleaning, including the removal of work trays and the disassembly of parts, were most often reported to be performed monthly in unclassified and ISO 7 or ISO 8 facilities and most often reported to be performed weekly in ISO 6 facilities. More than 80% of all facilities document the cleaning of their BSCs. Regarding rotation of cleaning agents, more than 70% of the unclassified laboratories and approximately 50% of all classified laboratories reported no rotation of these agents. Cleaning effectiveness was monitored in less than half (43%) of the non-classified laboratories but in the majority (approximately 70%) of all classified facilities. The methods used for testing cleaning effectiveness most often included surface swabs, microbial touch plates and particle counting. Information regarding sanitization of BSCs was not available from the previous survey. The currently reported practices point to a well-accepted standard operation of cleaning that includes a written SOP and documentation of sanitization procedures as well as a frequency of at least one daily BSC surface cleaning.

Large and small equipment

The survey divided equipment into two categories, large equipment (centrifuges, incubators, cell separators) and

small “moveable” equipment (pipettors, heat sealers, balances, tube racks). The intention was to ascertain whether laboratories have separate policies regarding different equipment types and sizes and whether they are treated with the same cleaning and sanitization methods. Questions were asked about cleaning large equipment such as incubators, centrifuges and cell separators and small equipment such as pipettors, balances, tube sealers, ring stands, test tube racks and so forth. More than 80% of all laboratories reported having SOPs for cleaning large equipment, and more than 80% of those labs reported documenting this cleaning as occurring daily, weekly, monthly and quarterly in all laboratory types.

The cleaning effectiveness of large equipment was tested by use of the same methods as mentioned above but performed in fewer than half of the classified laboratories and in only 14% of the standard facilities (unclassified). Rotation of cleaning agents was performed in approximately half of the classified laboratories but only in 19% of standard laboratories (unclassified).

SOPs for cleaning small equipment were reported in 60% to 91% of all laboratories, and 64% to 82% documented its performance. The most commonly reported frequency was before and after use, followed by the group that reported daily cleaning in all laboratory classes. More than 85% of the respondents do not test cleaning effectiveness of small equipment. Rotation of cleaning agents was similar to that of large equipment.

The use of tacky mats was not a standard procedure in unclassified facilities, and it was reported in only 21% of them, in contrast to 72% of ISO 8, 92% of ISO 7 and 40% of ISO 6 processing laboratories

use these mats. Lab coats, both reusable and disposable, were worn in most laboratories; a slightly larger percentage reported wearing reusable coats in the unclassified laboratories. Specific clothes/shoes (not “street” clothes), such as surgical scrubs, special shoes and so forth, were not used in most standard laboratories (75%), whereas special garb was worn in 62% to 75% of the classified facilities. Non-sterile gloves were worn in 80% of the unclassified laboratories and in 62% of ISO 8 laboratories, whereas sterile gloves were used in 51% of the ISO 7 labs and 83% of the ISO 6 laboratories. Hair bonnets as a rule were not worn in unclassified laboratories but were worn in all ISO-classified laboratories (63% to 83%).

Face masks reportedly were used in ISO 7 (69%) and ISO 6 (73%) facilities. Shoe covers were reported to be worn as the rule in all types of classified laboratories (59% to 89%). Sterile gowns and bunny suits were used in 50% of ISO 7 and 77% of ISO 6 laboratories.

General environmental monitoring

The responses to questions on environmental monitoring (EM) are summarized in [Figure 4A](#). Some of the questions were whether a facility performs EM and if they have a specific SOP for EM, if product release is tied to EM and if particle counts are performed. Most respondents do perform EM and have procedures in place to define it, and the percentage increases with ISO stringency. Written EM SOPs increased from 30% in the previous survey to 74% in the current survey for standard (unclassified) laboratories. Similar to the previous survey, particle counts are performed in almost all classified laboratories. Although fewer than half (43%) of the standard laboratories (unclassified) perform particle counts, this is triple the number of laboratories compared with the last survey. A new question asked was whether EM was a tied to product release, and it was reported to be important in the higher classified laboratories ISO 7 (40%) and ISO 6 (53%).

Specific types of contamination monitoring varied. Most respondents reported performing more microbial touch plate testing rather than air fallout (settle) plating for their laboratory spaces. Between 30% and 50% of the laboratories reported performing touch plate testing or swab tests either daily or weekly between class 100,000 and 10,000 laboratory spaces, with 50% of standard (unclassified) laboratories performing this procedure monthly. Fewer than 20% of the classified laboratories test their surfaces quarterly or less. Greater than 80% of the laboratories that never monitor were the standard (unclassified) laboratories. These comprised 20% of all the respondents to this question ([Figure 4B](#)).

There is a positive trend in monitoring surfaces in the unclassified standard (unclassified) laboratories, from overall less than 10% monitoring surfaces in the previous survey to 32% the current survey.

Cleaning staff

Cleaning was reportedly performed by the laboratory staff, the hospital cleaning staff or by outside contracted services. In the previous survey, the laboratory staff performed less than 10% of the sanitization/cleaning in unclassified laboratories, and this figure rose to 25% in the current survey. Similar to the previous survey, more than half of the class 10,000 and class 1000 laboratories reported that sanitization/cleaning was performed exclusively by the laboratory staff. Cleaning was performed in the standard (unclassified) and class 100,000 facilities by laboratory staff (54%), hospital staff (24%) or contracted services (22%).

Laboratory staff

A large number of facilities do not test personnel contamination, even though human presence is the greatest source of contaminants in a controlled laboratory environment. A total of 86% of respondents stated that they never test personnel in a standard (unclassified) laboratory. Standard (unclassified) laboratories process products within functionally closed systems inside BSCs. The figures for class 100,000, class 10,000 and class 1000 laboratories not testing personnel were 54%, 35% and 29%, respectively, whereas 32% of them test the staff during each product or work shift in class 10,000 laboratories and 43% in class 1000 laboratories. Because of inherent challenges in a survey of this type, this is not necessarily indicative of a laboratory not possessing proper controls. There are many reasons why these data may be acceptable on the basis of prudent risk management ideals performed before manufacturing activities.

Organism identification is performed by almost half of all respondents to the genus/species level. Others identify the organism by stain or morphology only and genus (averaging 12% and 20%, respectively). Approximately 14% perform no identification procedures whatsoever.

Staff training

Staff training is formalized and is required by regulatory and standard-setting organizations. In our survey, more than 90% of classified laboratories reported staff training documentation compared with more than 60% in unclassified laboratories.

Discussion

Although sanitization and cleaning effectiveness testing are not as stringent during early-phase research protocols and are of lower priority in clinical (closed systems) or early-phase clinical trials, facility sanitization is becoming more important to regulatory and accreditation bodies. GMPs require that facilities processing cellular therapy products be maintained in a clean and orderly fashion, in accordance with GTPs [6]. The cleaning and sanitation of a processing facility should be performed on a regular basis to prevent contamination and cross-contamination of products. Those facilities should therefore develop plans to assess sanitization practices and test cleaning effectiveness [7,8]. The type of processing needed determines the level of the processing environment. In the current survey, we summarize the practices of 132 laboratory respondents at 108 facilities spanning four continents and all levels of cellular therapy. The majority of laboratories (75%) of those who responded process minimally manipulated standard-of-care products. Conventional processing facilities do not require a classified environment for the facility, provided that processing steps are performed in a biological safety cabinet. Sanitization procedures and environmental monitoring remain issues to be addressed in all classes of laboratories. This survey was designed to determine the current status of cell processing facilities to provide necessary information for a forthcoming guidance document. We also compare the relevant results with those of a previous similar report in 2005 and added several more questions. Analysis of this survey may assist facilities in implementing a sanitization program.

According to the responses in this survey, the proportion of laboratories processing cellular products that use standard (unclassified) conditions was similar to that of the previous survey. These results support the notion that the relative number of laboratories that use unclassified air conditions is stable and that the types of laboratory assessments were very similar in both surveys, with 75% of those who responded processing minimally manipulated products that do not require special air quality. Standard air conditions are the most often used conditions for minimally manipulated HPC-A and HPC-M blood banking and HPC-C for thaw and infusion. The majority (59%) of cord blood products for banking were processed under stricter environmental conditions (ISO 6–8). This may be due to studies ongoing or regulatory policies, including FDA licensure, in the various institutions that process and bank cord blood. This possibility seems reasonable, given that some of these products will be cryopreserved for

many years. The replies clearly indicate that the more-than-minimally manipulated products and products under IND are being processed under stringent conditions. This survey also highlights positive changes in the involved regulatory bodies. The proportion of accredited laboratories did not change over the years in fields that have had very stable regulatory and accreditation requirements, such as CAP, for proficiency testing clinical laboratories. The number of laboratories that process products for cellular therapy has grown and is reflected by the dramatic increase in the number of FACT-accredited laboratories. The evident increase in the number of labs that are FACT-accredited (70%) and CLIA-accredited (43%) is encouraging and should affect better quality products. We know that hematopoietic stem cell transplant outcomes are better today than they were in the past, for numerous reasons. One must include the notion that increased laboratory accreditation may be an important contributing factor. The majority (95%) of all laboratories reported having a written QA program with SOPs that describe cleaning activities. However, most of the sanitization/cleaning SOPs were not based on any published standard, which indicates the need for standardization in the cellular therapy industry. The data validate the committee's (ISCT LPC) original desire to prepare these surveys and develop standardized cleaning practices to aid facilities in our industry to be more consistent, with the intent of better regulatory and accreditation compliance on this critical element. Standardization will, in turn, aid facilities in writing sanitization/cleaning SOPs and performing them in the most stringent and consistent manner possible. Surprisingly the data also reveal that no inspection by the governing regulatory body was performed in almost half of the facilities.

Testing the cleaning effectiveness and/or the cleaning process appears to be improved over the past years. More than half of the total laboratories do monitor the effectiveness of their cleaning procedure, with more than half of the unclassified labs testing their cleaning procedure. The numbers may even be higher because it is plausible that laboratories measured cleaning effectiveness of the entire laboratory without relating specifically to the area where cells were processed. Although it is encouraging that the number of standard facilities that do monitor their cleaning effectiveness has increased over the past years, more than half of the labs do not monitor the effectiveness of their cleaning procedures. Of those responding "yes" to microbial assessment, contact swabs or touch plates before and after cleaning and/or before and after sanitization

appeared to be the most commonly used method of assessment. This was used in almost all laboratories, with few actually doing microbial challenges. Many periodically (monthly or annually) contact test after cleaning. It appears that more monitoring with structured sanitization SOPs and follow-up documentation might be advantageous in those laboratories not performing this practice.

In addition to efficient air filters, physical barriers and cleaning techniques, the use of effective sanitizing agents is crucial to ensure the environmental quality of clean rooms. Standard sanitizing agents used were 70% solution of isopropyl alcohol, LPH and Vesphene (alkaline and acidic phenolic products), hydrogen peroxide solutions, sporklenz (peracetic acid, hydrogen peroxide and acetic), 1% Bioper solution and 5% phenol solution. Laboratories are rotating their cleaning reagents more frequently than reported in the past survey.

Cellular product manufacturing involves laboratory equipment. Cellular product preparation typically takes place in a BSC or laminar flow hood. As such, the BSC is one of the most critical pieces of equipment in the facility. Most laboratories have written SOPs for working in their BSCs, and cleaning is documented. Many laboratories clean/disinfect BSCs before and after each use with an appropriate cleaning agent. Following the manufacturer's instructions regarding the agent's minimal contact time before removal is paramount. More than half of the classified laboratories rotate their cleaning reagents. All laboratories reported BSC certification once or twice a year. Regarding large equipment, greater than 80% of respondents across all laboratory types have an SOP to describe equipment cleaning; 80% commented that they document cleaning. As mentioned previously, the past few years have seen an increase in FDA and accreditation emphasis on cleaning activities being written into a procedure and always documented. Another interesting point that emerged from this survey concerned the measurement of cleaning agent effectiveness compared with the more general question referenced above. Lack of testing for cleaning effectiveness appeared to be consistent throughout the survey. However, it is understood that many laboratories could have performed this activity laboratory-wide, just not specifically for equipment. Responses regarding questions on small equipment, unlike large, immobile equipment, showed a slightly smaller percentage of respondents, which indicates the presence of an SOP and documentation of cleaning (affirmative responses of 76% and 72.5%, respectively). A response regarding cleaning frequency before each use was about equal, although cleaning after a spill was slightly higher for small equipment. There were

fewer affirmative responses to testing cleaning effectiveness on small equipment across the different laboratory classes, which indicates that some facilities are performing a more global cleaning agent verification that covers all laboratory cleaning, whereas others may be more critically concentrating on certain aspects of lab operations.

EM of the facilities reported the wide use of settle plates, which has been determined to be quite ineffective in determining true airborne-viable particulate counts. Most microorganism-causing particles are 0.03 μm or less, which will not settle out of the air on their own and thus must be attached to a larger, non-viable particle to settle. The particle count is extremely low in highly conditioned and filtered clean room environments compared with non-filtered areas. The number of facilities that use some type of volumetric airborne sampling device was low. Class 100,000 facilities reported the use of these devices, with approximately 25% testing weekly, monthly or quarterly. Class 10,000 facilities were slightly less. Although the survey did not specifically address why a facility is not using these instruments, financial and/or staffing resources may be factors.

Regardless of a facility's risk assessment decisions addressing EM, every facility should have in place alert and action limits, parameters that indicate that certain predefined actions must be taken on the basis of EM results. Each facility is different, with dozens of parameters to consider. Design, construction, use, building air handling, product processing, reagents/supplies used and even local climate will dictate what each facility needs by way of an EM plan.

Conclusions

The vast majority of laboratories responding to the LPC's Facility Sanitization survey have a program for cleaning and sanitizing their facility. This represents an increase over the past few years since the previous survey in 2005. Additionally, their quality management system includes equipment, environmental monitoring and personnel practices designed to maintain facility compliance on the basis of the type of cellular products produced and the stringency of laboratory rules. Although many responses were not affirmative for some important issues, the reader should keep in mind that the survey could not provide enough detailed information to understand the reasoning behind this conundrum. It is the committee's desire that review of this survey will be helpful to ISCT members and other cell therapists providing information that will aid all facilities in producing the safest possible product for our

patients, thereby moving this growing field into the future of medical science. It is the aim of the LPC to use this survey to move toward creating a guidance document that can be used by cellular processing facilities across the globe.

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Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jcyt.2015.03.688>.