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CELLULAR THERAPY TRAINING

Training practices of cell processing laboratory staff: analysis of a survey by the Alliance for Harmonization of Cellular Therapy Accreditation

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Abstract

Background aims. Methods for processing products used for hematopoietic progenitor cell (HPC) transplantation must ensure their safety and efficacy. Personnel training and ongoing competency assessment is critical to this goal. Here we present results from a global survey of methods used by a diverse array of cell processing facilities for the initial training and ongoing competency assessment of key personnel. *Methods.* The Alliance for Harmonisation of Cellular Therapy Accreditation (AHCTA) created a survey to identify facility type, location, activity, personnel, and methods used for training and competency. A survey link was disseminated through organizations represented in AHCTA to processing facilities worldwide. Responses were tabulated and analyzed as a percentage of total responses and as a percentage of response by region group. *Results.* Most facilities were based at academic medical centers or hospitals. Facilities with a broad range of activity, product sources and processing procedures were represented. Facilities reported using a combination of training and competency methods. However, some methods predominated. Cellular sources for training differed for training versus competency and also differed based on frequency of procedures performed. Most facilities had responsibilities for procedures in addition to processing for which training and competency methods differed. Although regional variation was observed, training and competency requirements were generally consistent. *Conclusions.* Survey data showed the use of a variety of training and competency methods but some methods predominated, suggesting their utility. These results could help new and established facilities in making decisions for their own training and competency programs.

Key Words: *training, competency, cellular therapy product processing*

Introduction

Hematopoietic progenitor cell transplantation (HPCT) has recently reached the milestone of more than one million transplants performed worldwide [1]. This potentially curative therapy has been used for an increasing number of disorders over the past two decades [2]. As the field matures, it has sought both to regulate itself through adoption of voluntary accreditations [3–5] and has been subject to multiple national regulatory authorities. As a result, aspects of HPCT have become more standardized, although many differences in practices still exist. Standards and regulations specify

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overall training and competency requirements, and some accrediting bodies provide guidance, including examples of how to comply with standards but allow programs considerable freedom to adopt or adapt suggested training and competency methods. It speaks to the robustness of the field that there are multiple ways that programs can function while still achieving a high quality of care. However, the observed diversity in training practices can be confusing to new programs, and there are relatively few publications to provide guidance as to what works best.

The Alliance for Harmonisation of Cellular Therapy Accreditation (AHCTA) serves as the accreditation committee for the Worldwide Network for Blood and Marrow Transplantation (WBMT). To provide information and guidance to new programs, AHCTA recently published results of a limited international survey to describe HSCT program practices for training of staff that perform collection of two commonly used sources of hematopoietic progenitor cells (HPCs): umbilical cord blood (HPC(CB)) and HPC collected by apheresis (HPC(A)) [6]. The AHCTA has now completed a similar study of personnel training and competency assessment practices within cell processing laboratories that support transplant programs throughout the world. The results of this survey are presented here.

Methods

Survey questions were constructed to address the demographics of the different facility types that perform processing for HPCT programs including self-identified country affiliation, number of full-time employees, descriptions of staff and their educational requirements, and number and type of processing procedures performed. Multiple choice and open answer questions were used to determine the relative importance of training program elements and to determine methods by which competency was being assessed. The survey was conducted in 2013 to assess methods in place for processing performed in 2012.

The survey was delivered in an electronic format using a survey tool (Survey Monkey). Links to the survey were distributed to members of various organizations participating in AHCTA. Data were collected in the survey instrument and were imported into a database (Panorama, Proview Development) for ease of sorting, review and analysis of responses. The survey tool counted any entry regardless of the number of questions answered as a record. The 250 survey records were initially reviewed to eliminate those records for which there were no responses to the questions regarding training and competency practices. Records that contained partial information that was clearly identified as coming from a single center entered at different times were combined. A total of 182 records were further analyzed. Data were analyzed and graphed with computer software (Prism, GraphPad Software). The survey instructions requested that responses be limited to a single individual representing a processing facility, but no method was in place to ensure that this was the case. The number of respondents varied by question because there was no requirement to answer a question before proceeding to the next survey item. Several questions requested "all that apply" answer choices; therefore, totals for those questions did not equal 100%. Response choice percentages were calculated for facilities that responded to the question. Responses to individual questions generally exceeded 80% of the total 182 analyzed surveys. Due to survey design, self-selection and limitations in controlling responses, descriptive statistics were employed. Responses were categorized by major areas of the world as defined by the United Nations World Population Prospects to assess differences by region [7]. We further consolidated the data by combining regions when responses from a given single region were too few, as shown in Table I.

Results

Respondents characteristics

In total, 182 survey responses contained sufficient information for analysis. The analyzed responses represented 38 countries (plus 2 unidentified). The United States represented the largest number of responders from a given country at 76 (42.0%), followed by Germany at 16 (8.9%) and Italy at 11 (6.1%). The responses represent 45% of the 404 processing facilities currently accredited by Foundation for the Accreditation of Cellular Therapy (FACT) and Joint Accreditation Committee of the International Society for Cellular Therapy and European Society for Blood and Marrow Transplantation (JACIE) as published at their respective websites.

We used regions defined by the United Nations [7] to group countries. Because there were too few respondents from some regions, we combined all respondents into one of three grouped regions, Table I. We refer to these regional groupings as Group 1 (North America, n = 80), Group 2 (Europe and Oceania, n = 79), and Group 3 (Africa, Asia, Latin America, and unknown, n = 23).

The majority of all respondents were at academic medical centers (58%), followed by hospital-based facilities (21%) and blood center-based facilities (13%), the remainder represented cord blood banks that performed processing (7%) including two private cord blood banks, contract facilities (2%) or other (1%; physician's oncology office). The distribution of

Table I. Number of centers responding based on country, UN region, and region group.

Country	No. of facilities	UN region[a]
Region Group 1[b]	80	
Canada	4	North America
United States	76	North America
Region Group 2[b]	79	
Austria	2	Europe
Belgium	7	Europe
Croatia	1	Europe
Czech Republic	1	Europe
Finland	1	Europe
France	2	Europe
Germany	16	Europe
Greece	1	Europe
Ireland	1	Europe
Italy	11	Europe
Netherlands	7	Europe
Norway	1	Europe
Portugal	1	Europe
Russian Federation	1	Europe
Serbia & Montenegro	2	Europe
Slovakia	1	Europe
Spain	5	Europe
Sweden	2	Europe
Switzerland	2	Europe
United Kingdom	7	Europe
Australia	7	Oceania
Region Group 3[b]	23	
Algeria	1	Africa
Cambodia	1	Asia
China	2	Asia
India	1	Asia
Iran	1	Asia
Israel	1	Asia
Korea	1	Asia
Saudi Arabia	2	Asia
Singapore	1	Asia
Thailand	2	Asia
Argentina	1	Latin America
Brazil	1	Latin America
Colombia	3	Latin America
Mexico	1	Latin America
Uruguay	2	Latin America
Unknown[c]	2	Unknown

[a]United Nations Classification of Countries by Major Area and Region of the World, the 2012 Revision.
[b]Countries by region group.
[c]Facility location unknown.

facility types responding to the survey was similar for Group 1 and Group 2 but differed for Group 3 where there were a higher percentage of hospital-based sites (43%) than academic medical center–based sites (29%), and 14% were cord blood processing facilities. Respondents indicated their facility supported one (53%), two (17%) or more than two (30%) transplant programs. Academic and hospital-based facilities were most likely to support a single center, whereas blood centers, cord blood processing facilities and contract facilities most often supported multiple centers (Supplementary Figure 1).

Processing activity

To determine relative size of the facilities, respondents were asked to report processing activity for 2012 as a range of procedures (none, 1–50, 51–100, 101–200, 201–500, >500) by product and by donor type (autologous, allogeneic related, or allogeneic unrelated). Only 6% of respondents reported that they did not process products for autologous use during this period, 14% did not perform any processing of products from allogeneic related donors, and 16% did not process products from allogeneic unrelated donors. Respondents processing autologous products reported processing higher numbers of these products over the year than centers processing allogeneic products. The number of related and unrelated allogeneic products processed was similar with most (>60%) reporting 1–50 allogeneic products. The data included 14 centers that reported processing autologous products but not allogeneic related or unrelated products (not shown). Most of these centers (79%) processed only 1–50 autologous products in 2012 indicating that these were small autologous only programs. Only 6 of 150 facilities reported that allogeneic products were processed but not autologous products (4%) (Supplementary Table I).

Data on product source showed that HPC products including HPC(A), HPC(M) and HPC(CB) were processed by 89%, 72% and 54% of reporting facilities, respectively. Non-mobilized peripheral blood mononuclear cells collected by apheresis (MNC(A)) products and nucleated cells from marrow were processed by 59% and 14% of facilities, respectively and 49% of these facilities processed T-cell products to be used for donor leukocyte infusion. Usage of MNC(A) products and T cells was highest in Group 2 facilities and lowest in Group 3 facilities, other product usage was very similar across all groups (Figure 1 A,B).

The types of processing procedures performed by survey participants included cryopreservation with 87% using a controlled rate procedure and 22% using non-controlled rate methods (i.e., dump freezing) as a primary or backup freezing method. Non-controlled rate freezing alone was performed by 10% of sites making a total of 97% of laboratories performing cryopreservation. Most laboratories thawed products without further manipulation either at the bedside (71%) or in the laboratory (5%). Thawed products were also diluted before infusion primarily within the laboratory (33%) and 39% of facilities reported thawing and washing away cryoprotectant reagents within the laboratory before infusion. Plasma reduction either for minor ABO incompatibility or to reduce

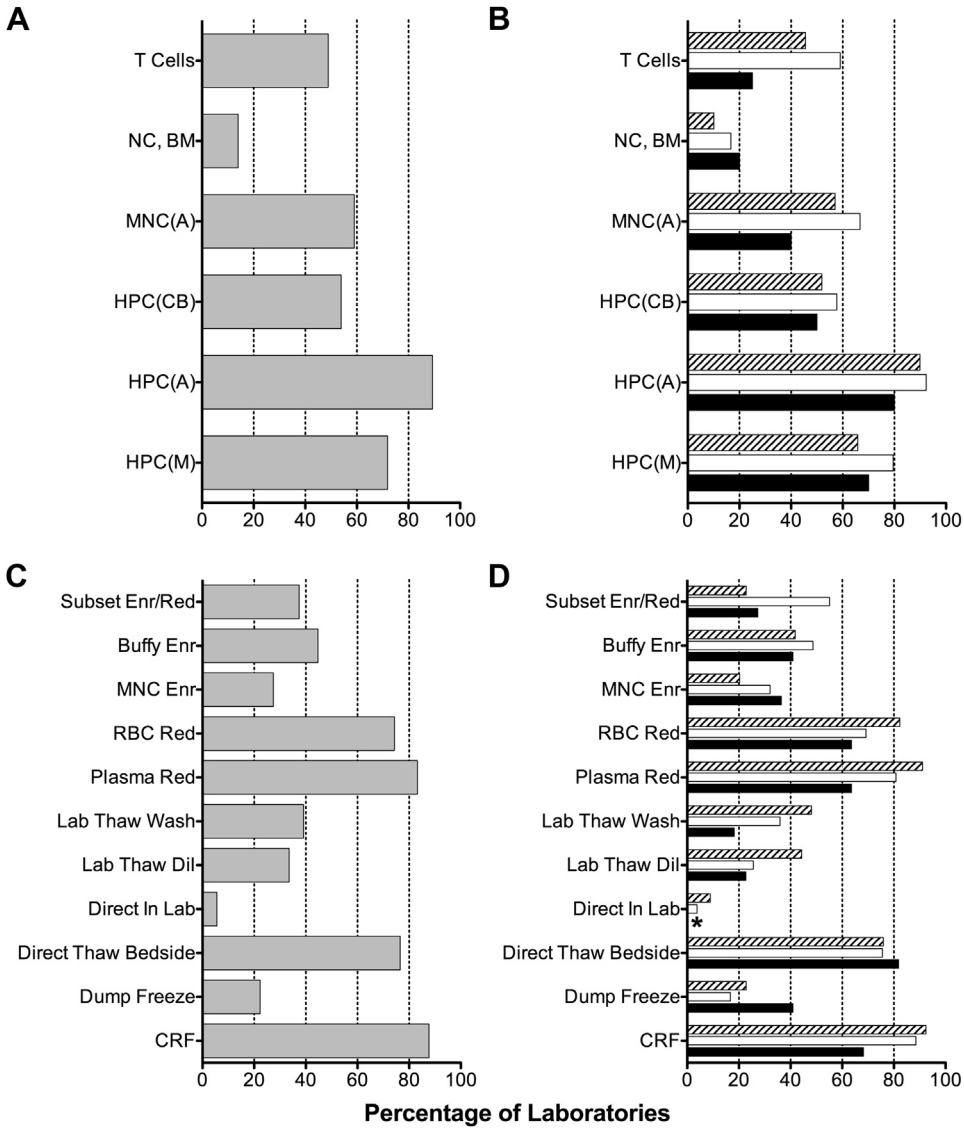

Figure 1. Types of products processed and processing procedures performed. Data are expressed as the percentage of total responses for product source (A), responses by region groups for product source (B), total responses for processing procedures (C), and responses by region group for processing procedures (D). For data by group: hatched bars, Group 1; open bars, Group 2; black bars, Group 3. *None reported.

product volume was performed by 83% of facilities, and some form of red blood cell reduction was performed by 74% of laboratories. MNC enrichment and buffy coat enrichments were performed by 29% and 44% of facilities, respectively. More than a third of 180 respondents (37%) performed subset enrichment or reduction using devices. Other manipulations reported by the survey sites include T-cell depletion using Campath added to the product bag, purging through positive selection, and the production of platelet-rich plasma (Figure 1C).

Processing procedures were also analyzed based on defined region groups. A similar percentage of laboratories performed a direct thaw at the bedside (76% of Groups 1 and 2, and 82% of group 3). Facilities in Group 1 were more likely to thaw in the laboratory using either dilution or wash methods with 45% doing each method, whereas 23% of Group 2 and Group 3 laboratories thawed with dilution. Thawing with washing was least likely to occur in Group 3 facilities at 18% compared with 48% for Group 1 and 36% for Group 2. Plasma reduction and red blood cell depletions were more commonly performed in Group 1 facilities (>80%) and least likely for Group 3 (<64%). More subset enrichment or depletion using devices were performed in Group 2 facilities (55%) versus <28% in Group 1 and Group 3, as shown in Figure 1D.

Staffing requirements

The surveyed facilities employed from 0.5 to >8.5 full-time equivalent (FTE) employees to perform or oversee processing of minimally manipulated products, with most reporting 1.5–2.5 (36%) FTE employees or 3–5.5 (33%) FTE employees. There was some difference by facility type for overall FTE commitments. Hospital-based facilities (21%) reported having only 0.5–1.0 FTE employees devoted to processing, whereas cord blood banks were far more likely to have >8.5 FTE employees (33%). Three of four contract facilities responding to the survey indicated staffing included only 1.5–2.5 FTE employees for performing or overseeing processing of minimally manipulated products. However, when all activities within the contract laboratory were considered, FTE technical staff numbered 2–3 or 4–6 for 75% of the labs reporting. The number of FTE employees by location was also analyzed. Region Group 1 and Group 2 facilities were similar with 45% and 43% of facilities with <3 FTEs compared with 53% in Group 3 (not shown).

A more detailed breakdown of FTEs to the nearest 0.5 FTE employee for each of the main laboratory positions was requested for all activities for which the processing facility was responsible. The majority of facilities reported that less than 1 FTE employee was assigned for the medical director or the director positions, indicating that individuals in these positions also had responsibilities outside the laboratory. Overall, approximately 10% of facilities reported having no FTE employee allotted to the medical director and director positions. Given that standards require both positions, it may be that respondents indicated no medical director or director in cases in which these positions were occupied by the same individual (although that was not the intent of the survey), rather the percentage of time in each role should have been listed. A few facilities (<2%) indicated that the medical director and director positions were occupied by 2–3 FTE employees. In total 58% of respondents indicated that 1 FTE occupied the role of laboratory manager or supervisor; another 22% had 0.5 FTE employees in that position, and 14% had none or <0.5 FTE employees dedicated to laboratory management or supervision. For 6% of facilities, 2–3 FTE employees were dedicated to laboratory management or supervision. More than 70% of facilities had >1 FTE employee designated as technical staff, with most having between 2–6 FTE employees (61%). Overall staffing requirements are presented in more detail in Supplementary Table II.

The major differences when analyzed by region were the lack of a designated medical director reported by approximately 11% of facilities in Group 1 and Group 2, compared with none of 19 responding facilities from Group 3. None of 18 responding Group 3 facilities lacked a designated laboratory manager or supervisor (data not shown).

Training methods

Facilities reported performing training using more than one method, but certain methods were employed more commonly than others. More than 90% of 177 respondents reported that newly trained staff completed an introduction to the facility's organization and structure (orientation program) and safety training, and 73% required new staff be trained in current Good Manufacturing Practices (GMP) or Good Tissue Practices (GTP). The percentage of facilities requiring orientation, safety and GMP training was highest for geographic Group 1 (97.4%, 98.7% and 83.3%, respectively) and 9–16% lower for Group 2 (87.0%, 89.6% and 67.5%, respectively). Group 3 countries were 12–24% less likely than Group 1 to perform all three areas of training for newly hired staff (81.8%, 86.4% and 59.1%, respectively).

For commonly performed procedures, the most frequently used training method was for staff to observe procedures and then be observed performing those procedures (87%). A specified minimum number of each type of commonly performed processing procedure was required at 60% of responding facilities, and 50% of facilities reported that training requirements were tailored based on previous experience. The need to pass a written test to be considered trained was required at 33% of facilities, and the need to read and discuss published articles relative to processing was required by 40% of facilities (Figure 2A). Only 25% required that training be completed by a minimum defined time limit, and only 0.6% of respondents indicated no specific training requirements were defined. Regional differences are shown in Figure 2B. More facilities in Group 2 required completion of a minimum number of procedures before being considered trained, whereas Group 1 facilities were more likely to require passing test scores. Adjustment of training requirements according to the previous experience of the individual was more likely to be seen in facilities located in regional Group 3.

In total, 99 respondents indicated that training required completion of a minimum number of procedures, and most indicated a minimum required number of 2–5 (48%), whereas 34% required minimally 5–10 procedures. The fewest respondents (14%) required >10 procedures as a minimum to be

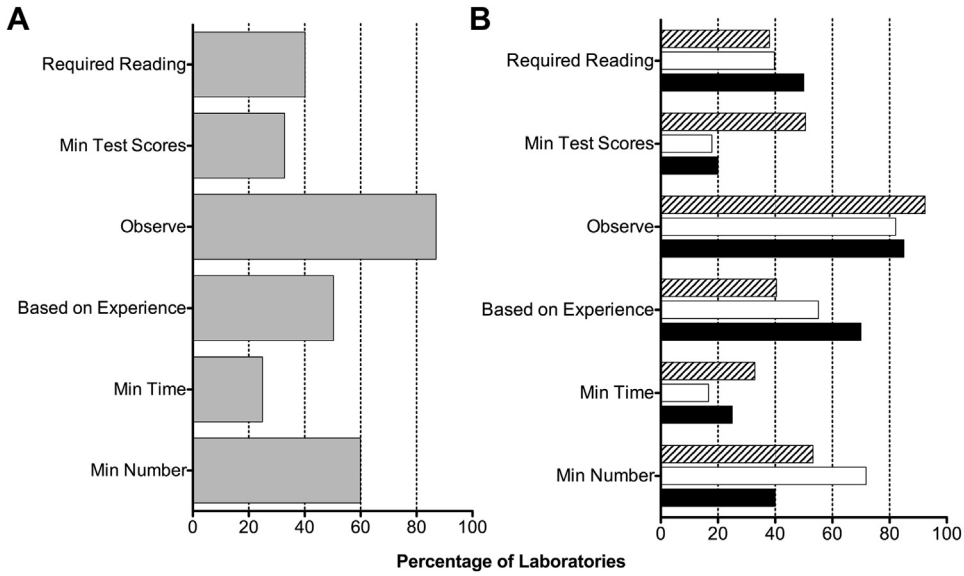

Figure 2. Training methods overall and by region groups. Percentage of facilities reporting the use of the indicated methods for staff training: overall (A); data by group (B): hatched bars, Group 1; open bars, Group 2; and black bars Group 3.

considered as trained. Group 2 and Group 3 facilities were more likely to require >5 procedures as the minimum number than was Group 1 (not shown). For 49 facilities that indicated a minimal time for training, most required 9–12 weeks (35%). Other choices were 1–4 weeks (14%), 5–8 weeks (25%), and 13–26 weeks (27%). Group 3 facilities that defined a minimum time for training (n = 7) were more likely to require a shorter minimum training period of <9 weeks (57%) than Group 1 (n = 21) or Group 2 (n = 21) at 38% and 33%, respectively (Supplementary Figure 2).

Cell sources for training

The survey included questions to identify sources of cellular materials used for training and how this might differ from frequently performed procedures and those less commonly performed, given that standards require staff performing any procedure, regardless of frequency, be trained. Overall, products for clinical use (78%) or mock products (64%) were predominately used to train staff on common procedures. Group 3 facilities also used these sources but were more likely than the other two groups to also use products collected under research protocols (25% versus 13% and 21% for Group 1 and Group 2, respectively; not shown). Of the 177 respondents, 56% indicated that training product sources and methods did not differ based on how frequently the procedure is performed, 40% said there would be differences, and 4% did not know. Those sites that responded training would differ for rare procedures (n = 71) indicated that fewer staff members would be trained or the duration of the training period would be increased (38%) and that fewer clinical products would be required to be processed under supervision (55%) than for more commonly performed procedures (78%) (Table II).

Few (<2%) facilities in Group 2 used purchased products for either common or less common procedures, whereas approximately 24% of Group 1

Table II. Training products used for common versus rare procedures.

Product or method used for training	Common (n = 177)	Rare (n = 71)
Entire products intended for clinical use (with supervision)	78.0%	NA
Mock products (e.g., expired blood units, buffy coat discard products, negative fractions from cell selection or depletion, etc.)	63.8%	63.4%
Purchased products (e.g., mobilized apheresis products from a commercial source)	11.9%	12.7%
Products collected under facility or institutional quality controls or research protocols	15.3%	12.7%
A portion of a product collected for clinical use	17.5%	14.1%
Fewer staff trained or increase duration of training	NA	38.0%
Fewer entire products for clinical use required (with supervision)	NA	54.9%

Respondents were asked whether there were differences in the products used for training for commonly performed procedures compared to processing procedures that were rarely performed. Those indicating a difference were asked to select methods used for rare procedures. n, the number of facilities responding to the indicated question.

facilities purchased products for training regardless of how common the procedure was. Region Group 3 reported using purchased products for less commonly performed procedures in 20% of facilities versus 5% for common procedures (data not shown).

Competency assessment

Competency assessment after initial training was performed yearly by most facilities. Several facilities indicated that a 6-month competency assessment after initial training was required, with assessment yearly thereafter. However, because of an error in skip logic, only those respondents who indicated that training requirements for less frequently performed procedures were the same as those for commonly performed procedures had access to this question (Table III).

The methods used for competency evaluation were surveyed. Because only a subset of respondents for the previous question regarding the interval for competency assessments had access to this question, a total of 70 individuals responded. The most commonly used method was direct observation of personnel while they performed clinical procedures for adherence to written procedure (80%) followed by evaluation of product quality over the assessment period (76%). Other methods included written assessments (51%), employee review of all relevant procedures (47%), use of mock or test products (23%) and review of yearly proficiency test results (69.5%) (Supplementary Figure 3). Because of the lower number of total respondents to the broader competency questions, regional differences were not analyzed because there were only five responses from Group 3 facilities.

All survey respondents had access to follow-up questions to determine which product parameters were assessed if evaluation of product quality was used as a measure of competency. A total of 128 individuals indicated that product quality was used as a measure of competency (76% of all respondents), whereas 41 indicated that product quality was not used. The three most common parameters assessed were recovery of CD34+ cells (80%), product sterility (97%) and product viability (84%). Other product characteristics assessed for staff competency included mononuclear cell recovery (42%), recovery of colony forming units (CFUs) (31%), product volume (25%), target cells other than CD34+ cells (such as T cells or B cells) (25%) and hematocrit (23%). Total nucleated cell recovery was specified by four respondents as a parameter not included in the choices that was monitored as part of staff proficiency. Marked differences based on region were not seen (Table IV).

Of 116 respondents who considered the results of proficiency testing in assessing competency most used external proficiency studies (eg, CAP, StemCell Technologies; NEQAS, etc.) (73%), followed by internal proficiency studies (within the laboratory) (56%), and Inter-laboratory proficiency studies (26%). External proficiency was most likely to be used by Group 1 facilities (81%) compared with Group 2 (70%) and Group 3 (54%), whereas Group 1 facilities were less likely to use internal proficiency studies (47%) than Group 2 (67%) or Group 3 (62%). Inter-laboratory exchanges were most often used by Group 3 (46%) facilities, compared with Group 1 (17%) and Group 2 (31%).

Actions taken when a staff member fails to demonstrate competency were also assessed. These actions included mandatory retraining for 84% of 172 respondents to this question. The nature of retraining was customized (55%), included a period of direct supervision before staff could process independently (54%), required staff to document review of all applicable processing procedures (41%) or required staff undergo full retraining (26%). No regional differences were seen for this question.

Requirements and responsibilities

Standards applicable to staff training require that facilities determine minimal requirements needed for an individual to serve as a trainer but do not specify what those requirements should be. This survey addressed that issue by asking facilities to choose from a list of possible requirements. The data in Figure 3A indicate that training with a minimally designated period of relevant experience was the most common minimal requirement for a trainer

Table III. Competency assessment intervals.[a]

	As needed	Biannual	Yearly	Every 2 years	Performed but not specified	Not performed	Total response
Managers/supervisor	6.3%	1.6%	63.5%	4.8%	7.9%	15.9%	63
Technical staff	6.0%	6.0%	74.6%	3.0%	4.5%	6.0%	67
Other staff	13.8%	10.3%	51.7%	3.4%	10.3%	10.3%	29

Data represent the percentage of responding facilities.
[a]Because of an error in survey design, only respondents who indicated that training differed for less commonly performed procedures responded to this question.

Table IV. Aspects of product quality used for competency assessment.

Product characteristic	Group 1	Group 2	Group 3	Overall
CD34 recovery, %	70.9	83.9	94.1	79.7
Product sterility, %	98.2	98.2	88.2	96.9
MNC recovery, %	47.3	33.9	52.9	42.2
Target cell recovery not CD34, %	20.0	28.6	29.4	25.0
CFU, %	21.8	44.6	11.8	30.5
Volume, %	14.5	32.1	35.3	25.0
Hematocrit, %	14.5	28.6	35.3	23.4
Viability, %	81.8	87.5	76.5	83.6
Other, %	1.8	3.6	5.9	3.1
Number answered	55	56	17	128

Data are the percentage of facilities responding when product quality is evaluated as a measure of staff competency.

(54%) followed by any staff members who were themselves trained (50%), manager/supervisors (40%) or those staff members who were experienced individuals who may not have undergone formal training (grandfathered) (37%). Requirements that trainers minimally must serve as director or medical director or a trained individual who served a quality management role were required at 19% and 16% of the survey respondent institutions, respectively. Only 2% of facilities had no minimum requirements for trainers in place. Additional requirements at several facilities included that before being designated as an independent trainer, the individual needed formal classroom instruction in training and/or be observed as they train other staff. Others indicated that some trainers may be approved only for certain procedures with which they had long-standing relevant experience. As shown in Figure 3B, there were differences based on location with more centers in Group 3 requiring minimally that the laboratory manager, directors, or quality management staff bear responsibility for training.

The position of key personnel with overall responsibility for staff training and competency was also assessed in the survey. Laboratory managers or laboratory supervisors were most often indicated as having responsibility for both activities (reported by greater than 60% of respondents) followed by technical staff designated as trainers (55%), then by laboratory directors (reported by approximately one third of respondents). Medical directors and quality management personnel reporting to laboratory management also had responsibility for training and management (18% and 26%, respectively) with quality management personnel not reporting to laboratory managements involved in these activities at <5% of facilities. Technical staff designated as trainers were somewhat more likely to have training rather than competency assessment responsibilities (Figure 4A,C). Regional differences were seen especially in regards to the role of the medical director in training and competency assessment within the laboratory (Figure 4B,D). None of the Group 1 facilities reported medical director involvement in training, and only 13% indicated that this position was involved with competency assessments. This was in contrast to >31% involvement in both activities in Group 2 and Group 3 facilities. Facilities in Group 1 were also more likely to designate responsibility for training and competency to the Laboratory Manager. Comments to these questions indicated that the

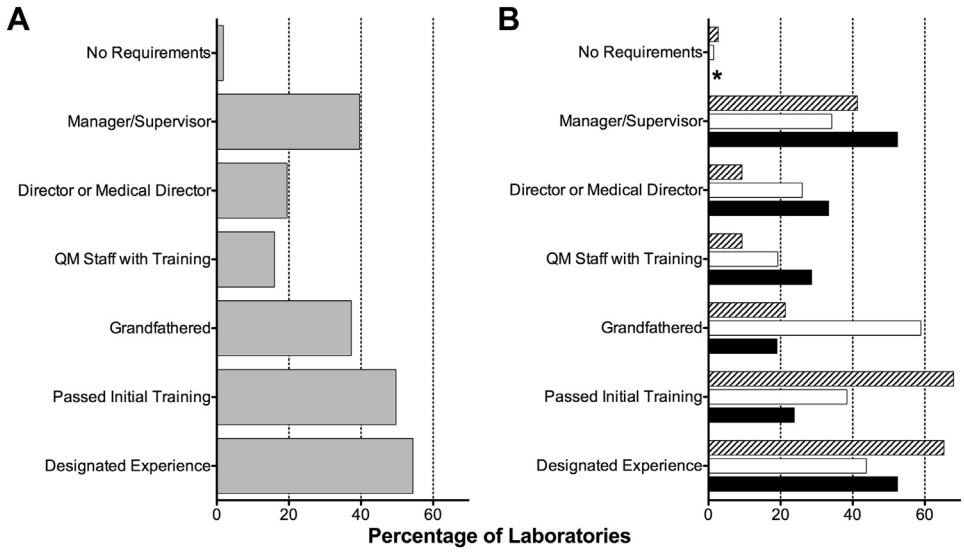

Figure 3. Requirements to be a trainer. (A) Percentage of overall respondents reporting minimum trainer requirements. (B) Percentage of respondents within each group reporting minimum trainer requirements. Hatched bars, Group 1; open bars, Group 2; black bars, Group 3. *None reported.

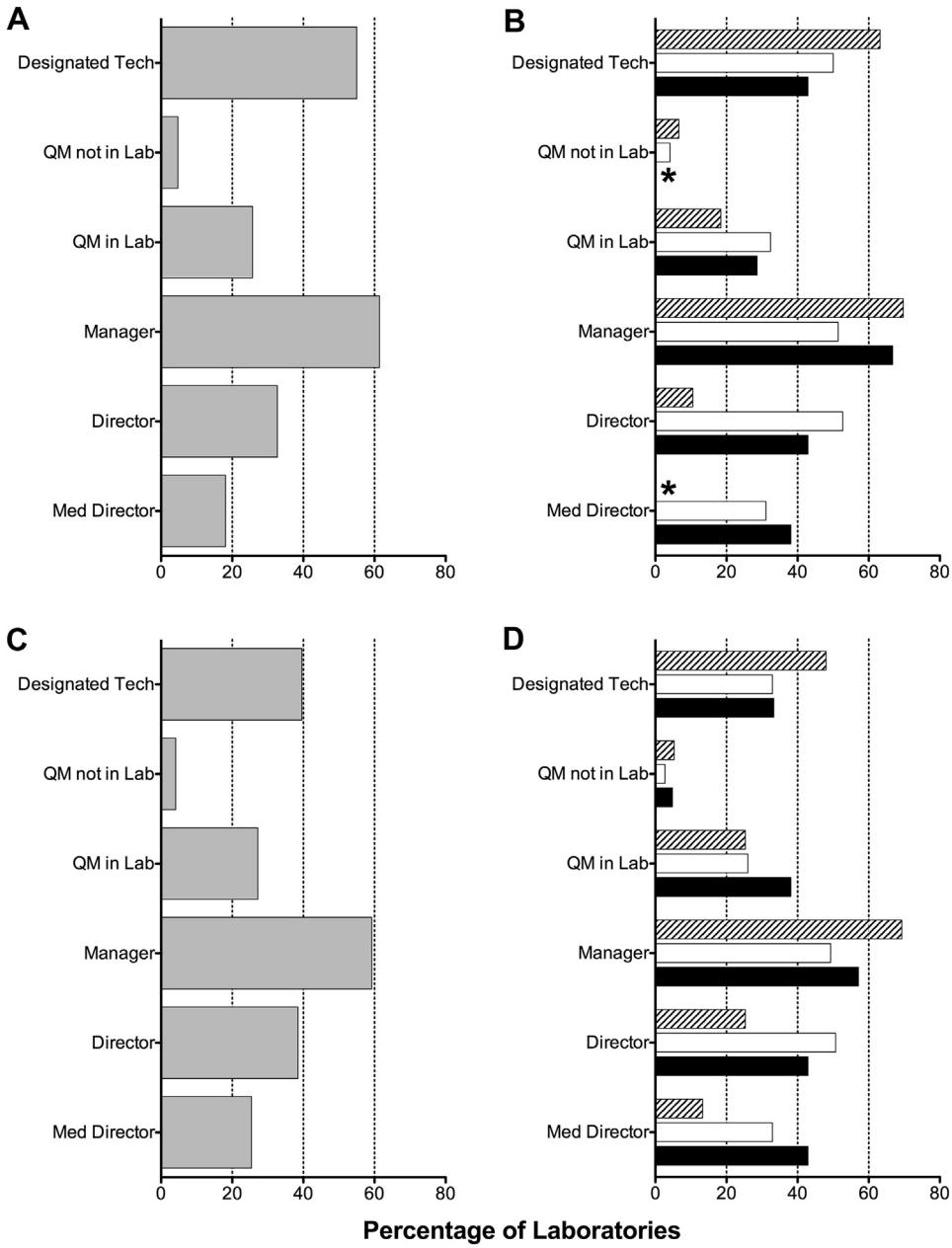

Figure 4. Responsibilities for training and competency. Facilities were asked to indicate the positions within the laboratory responsible for performing or overseeing training. Data are the percentage of overall responsibilities for training (A); training by region group (B); overall responsibilities for competency assessment (C); and competency assessment by region group (D). For data by group: Hatched bars, Group 1; open bars, Group 2; black bars, Group 3. *None reported.

Laboratory Directors and Medical Directors were more likely to provide training in theoretical background of processing and transplantation as well as review and approval of training and competency records.

Additional staff responsibilities and methods for training

Processing laboratory staff may also have responsibilities other than those limited to product processing. The survey focused on several of these activities to determine activity frequency within the respondent pool. Four of the survey activities were the responsibility of $> 85\%$ of reporting facilities. These included procedure and process validation (95%), materials management (95%), equipment qualification and maintenance (91%) and product testing (87%) (Figure 5).

Only 9 of 171 respondents (5%) indicated their facilities played no role in materials management. More detailed questions indicated that most laboratories were responsible for ordering materials (83%),

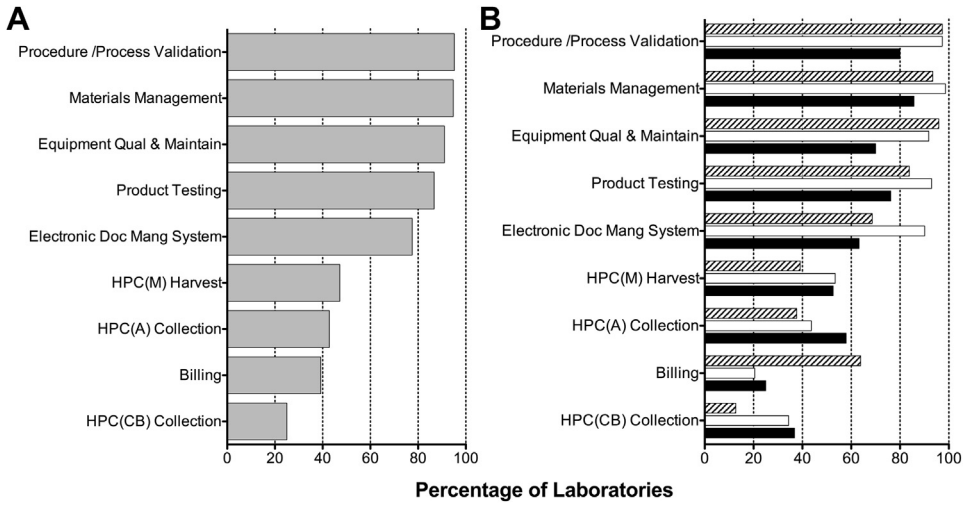

Figure 5. Other laboratory responsibilities. Laboratory responsibilities in addition to processing. Overall responses (A); responses by region group (B). For data by group: hatched bars, Group 1; open bars, Group 2; black bars, Group 3.

documenting receipt of materials (85%), reviewing and releasing materials for use within the laboratory (78%) and managing records of material use (e.g., lot records) (88%). Vendor qualification was the responsibility of only 39% of facilities. Differences between groups were seen for overall responsibility for materials management with 7% of Group 1, 1% of Group 2, and 14% of Group 3 regions having no responsibility for this activity. Responsibility for vendor qualification fell to only 31% of Group 2 facilities, 43% of Group 1 and 52% of Group 3 (not shown).

Of facilities that performed product testing (87%), product cell counts using a hematology analyzer was performed in 74% of facilities, followed by inoculation of sterility cultures (67%), product phenotype by flow cytometry (47%) and performance of colony forming assays (46%) and sterility culture detection of growth (22%). Less commonly performed tests included hematocrit using a centrifugation method (10%), endotoxin testing (8%), gram stain (8%) and sterility culture organism identification and antibiotic sensitivities (8%) (Figure 6A). Viability testing by trypan blue or using flow-based assays was not included as an answer choice but was indicated by a number of respondents as a common product test. Indeed, most often flow phenotyping would include viability testing. Testing responsibility was also analyzed by region group and by facility type for the top five testing procedures performed. The data in Figure 6 (panels B and C) shows that all groups were equally likely to be responsible for cell counts using a hematology analyzer but that facilities in Group 1 were less likely to be responsible for product phenotype and more likely to inoculate sterility cultures than Group 2 or

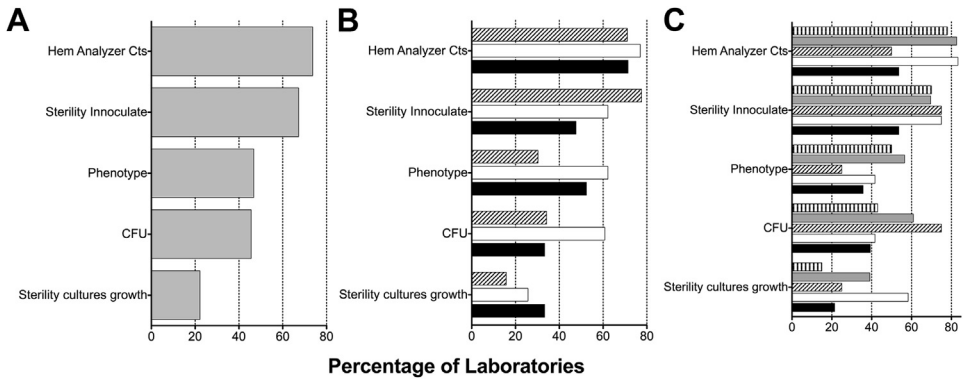

Figure 6. Testing performed within the laboratory, overall, by region, and by facility type. Shown are the five most common testing procedures performed by facilities responsible for product testing. Data are shown overall (A); by group (B); and by facility type (C). More than one choice was allowed. For data by group: hatched bars, Group 1; open bars, Group 2; black bars, Group 3. For data by facility: vertical stripped bars, academic medical center–based; light gray bars, blood center–based; hatched bars, contract facility; open bars, cord blood processing facilities; black bars, hospital-based facilities.

Group 3. Group 2 facilities were more likely to be responsible for product phenotyping and to perform CFU assays than other groups. Group 3 facilities were least likely to inoculate sterility cultures within the laboratory. When looking at facility type, it appears that hospital-based facilities are less likely than other facility types to inoculate sterility cultures, contract facilities were most likely to perform CFU assays and less likely to perform product phenotype (but with n = 4), and blood center–based facilities were most likely to perform product phenotyping. Note that these data do not mean the surveyed assays were not performed on processed products, but rather that the tests were not performed within the processing facility.

Overall, facilities were least likely to be responsible for cord blood collection, billing, or apheresis or marrow collections. Regional differences were seen for billing with Group 1 facilities having billing responsibilities 64% of the time, whereas Group 2 and Group 3 had this responsibility 20% and 25% of the time, respectively. For procedure or process validation, Group 3 facilities were not responsible for this activity 20% of the time compared with <3% of the time for Group 1 and Group 2. Group 2 and Group 3 facilities were approximately 15% more likely to have responsibilities for apheresis and marrow collection than Group 1 facilities. Cord blood collection was performed by Group 1 facilities only 13% of the time compared with approximately 35% of the time for Group 2 and Group 3 facilities. Electronic document control systems seemed to be widely used in cell processing facilities with participation ranging from 90% in Group 2 to a low of approximately 68% of Group 1 and Group 3 (Figure 6B).

Despite differences in responsibilities, few regional differences were seen in the method through which staff members were trained for these responsibilities. For activities performed within the laboratory, training is primarily performed by trainers who are part of the laboratory staff. A larger percentage of facilities use trainers who are not part of the laboratory staff as trainers for product collection activities and for training in electronic document management systems. Equipment qualification and training for apheresis collections are more likely to depend on externally trained trainers to come onsite for staff training. It is rare for staff to leave the facility for training, although this does occur in 7% of facilities responsible for testing (Table V).

Respondents were asked to provide information on training methods other than those listed used in staff training. Responses included: the following

- Having biannual external trainer for changing relevant activities.
- Sending staff at start-up facilities to established centers for full training.
- Requiring retraining for procedures not performed at established frequency.
- Specific training for aseptic technique (e.g., media fills).
- Compare product parameters among staff members.

Discussion

The AHCTA is supported by 16 organizations active in the field of HPCT and aims to harmonize standards regulating HPCT. Crosswalk documents of cell therapy standards are published on its website [8]. Patient outcomes appear to have benefited from the establishment of a quality system in centers accredited under the FACT/JACIE standards [5,9]. General personnel requirements for training and

Table V. Training methods for non-processing activities within the facilities.

Activity	Percent responsible for activity	Training method for participating facilities			
		Experienced trainer within facility	Externally trained trainer within facility	Externally trained trainer comes to facility	Trainee leaves facility for training
Product testing	86.7	97.9	2.1	4.2	7.0
Materials management	94.7	97.3	2.0	1.3	1.3
Billing	39.2	95.4	4.6	0.0	1.5
Equipment qualification and maintenance	91.0	94.0	6.0	18.5	4.0
Procedure or process validation	95.2	96.2	4.4	6.3	4.4
HPC, apheresis collection	42.8	85.3	16.2	27.9	4.4
HPC, marrow harvest	47.2	92.1	6.6	2.6	1.3
HPC, cord blood collection	25.0	90.0	10.0	0.0	5.0
Electronic Document Management System	77.5	91.7	12.1	12.1	3.2

The data presented show the percentage of responding facilities that indicated they participated in the non-processing activities shown and for those facilities participating in an activity, the training methods used.

competency are specified in standards from FACT/JACIE, FACT/Netcord and the American Association of Blood Banks. The requirements of these standards were used as a starting point for survey questions to get a clear view of what methods are used in facilities all around the world.

HPCT is most commonly available in developed countries, particularly in North America, Europe and Australia [2]. However, as shown by this survey, HPCT is clearly becoming available worldwide. Indeed, the AHCTA working through its parent organization, the Worldwide Network for Blood & Marrow Transplantation, made a directed effort to ensure that the survey was available to established processing facilities in less developed countries. As a result, we feel that this survey represents the scope of processing activities and of current practices for training and competency assessment as performed in processing facilities worldwide. The responses represent a good distribution of facilities from small to very large shown by the processing activity reported. Individual facilities processed most, if not all, of the common sources of HPC products used for transplant. HPCT has progressed in the past two decades from an experimental approach to standard of care for the treatment of many diseases. However, the survey revealed that most processing facilities remain based in academic medical centers (58%). Instituting practices to ensure staff members are properly trained and competent to process products suitable for clinical use has been a challenge for some facilities. There are a multitude of roles processing facilities play within the transplant program. Unlike an earlier survey of training and competency methods used for apheresis and cord blood collection [6], we had a sufficiently large and diverse worldwide response that we were able to analyze data using three major defined region groups to determine whether there were differences in practices based on location. We recognize that differences in response by region might also reflect the facility types given that the distribution of facility types was not equal. Group 3 contained proportionally more hospital-based facilities and cord blood processing facilities and fewer academic medical centers than Groups 1 and 2. Groups 1 and 2 were more evenly matched. There were insufficient responses to perform sophisticated multi-variant statistics, and therefore the differences we report are descriptive and may not be statistically significant. Where facility type was of potential importance to a response, we performed a separate analysis to assess this. However, the primary focus was on overall response to the survey questions and responses based on region.

Regional differences were not seen to any great extent in regard to source of the HPC products processed between any of the groups. Group 3 facilities did report processing fewer products intended for non-HPC use, such as donor leukocyte infusion, compared with Groups 1 and 2. It could be that donor leukocyte infusion is less likely to be used outside North America and Europe, although there were fewer respondents in Group 3, so this remains to be determined. Processing activity differences were also seen for controlled rate freezing methods, with less activity in Group 3 facilities. This may reflect more difficult access to the sophisticated and expensive equipment that is required. A higher percentage of Group 2 facilities reported performing subset enrichment or depletion using devices, likely representing the approval in Europe of the Miltenyi CliniMACS devices that were exclusively being used under regulatory approvals outside of Europe in 2012.

It was reassuring to find such a high percentage (>90%) of facilities reporting initial training programs that included orientation to the facility and laboratory safety training with a smaller (73%) but still significant number including GMP or GTP training. The training methods used in the laboratory are much like those used for staff collecting apheresis products or cord blood, and not surprisingly, a similar percentage of processing facilities reported using these methods [6]. Direct observation of procedures by staff and observation of staff by trainers was the most commonly used approach by facilities regardless of geographic group. Requirement for a minimum number of procedures to be performed was the second most frequent training method. Predefining a time for training was less often used likely because the frequency of training opportunities will vary within a defined time span and full training may not be achieved. However, a defined timeline may be a useful way to identify individuals who are not likely to meet expectations. Many facilities customize training criteria based on specific experience of the trainee. Because of the variety of procedures performed, a combination of training methods were used in all laboratories surveyed. Group 3 facilities were as likely as Group 1 and Group 2 facilities to use the same criteria to consider staff as trained.

Many facilities perform a given procedure only rarely. Typically, these might be subset enrichment or depletion using specialized devices for which only a few patients per year are eligible. Products needed for training might not be readily available, especially if mobilized products are required. We assessed the accommodations that were used to train personnel for rare procedures. Responding facilities indicated that product sources did not differ to a significant degree from more common processing procedures. However, training more often took longer and/or

fewer staff would be trained. Centers used often-expensive purchased products for training for both common and rare procedures, although this option was generally limited to rare procedures for Group 3 facilities.

Standards and regulations often focus on the importance of initial training, but maintaining staff competency is also essential. Because of an error in survey skip logic, questions regarding competency assessment intervals were not available to 44% of survey respondents. As a result of the lower numbers, assessment of responses by region group was not possible. Most accreditation bodies require yearly competency assessments, so, not surprisingly, assessments were performed this often or more frequently. Unlike training, there were facilities that indicated competency assessment was not performed. This was more common for managers or supervisors and nontechnical staff than for technical staff. The tools used for competency assessment were broader in scope than for initial training in that they could include a review of processing outcomes and results of proficiency testing. Indeed, three quarters of respondents used product parameters, including CD34+ cell or other target cell content when relevant, and nearly all facilities considered product sterility and viability as a measure of competency. Within the laboratory, between laboratories, and external graded proficiency studies were all used for competency assessment. Nearly all respondents indicated that methods were in place to retrain staff failing to meet competency requirements with a required period of retraining as the most frequent corrective action.

Responsibility for training differed from competency in that trained and qualified technical staff had the major role in training, but a lesser role in competency assessment. laboratory directors and even medical directors were reported to play a greater role in competency assessment. Given that training is a more prolonged process than competency assessment and requires a larger time commitment from the trainers, it is not surprising that directors play less of a role. Competency assessment in contrast is typically done in a more defined period of time and, as reported in this survey, often involves review of processing outcomes and performance in proficiency testing. These are activities that are typically directly overseen by laboratory leadership.

This survey also revealed the large extent to which laboratories bear responsibility for performing activities outside of product processing. More than 86% of survey respondents reported their laboratories had responsibilities for performing product testing, materials management, equipment qualification and maintenance and procedure or process validation. Billing was the non-processing responsibility that differed the most by region. Facilities in Group 1 (North America) were most likely to have billing responsibilities (64%) compared with Group 2 (20%) or Group 3 (25%) likely due to differences in health care delivery systems. Although all of the activities surveyed appropriately fall under the responsibility of the laboratory, performance of many of these functions may be external to the laboratory. When allotting resources to the processing facility the non-processing activities performed by laboratory personnel need to be considered and appropriate training and competency programs established.

In summary, our survey showed that training and competency programs are well established in cell processing facilities worldwide, with most facilities using similar methods for both. Data from this survey can provide useful guidance for newly established facilities by showing which training and competency methods are most commonly used and may assist established facilities wishing to improve existing programs.

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Supplementary data

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