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Review article

Standardization of cellular therapy terminology, coding and labeling: a review

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ABSTRACT

The 1990s saw rapid growth in international activity in hematopoietic cell transplantation. As national donor registries were established and international collaboration increased, a need to transfer cellular therapy products across national borders emerged. A lack of international standards for identification, terminology and labeling resulted in significant challenges for import and export. Twenty years of effort by a large group of experts supported by professional societies and accreditation bodies has today achieved a high degree of standardization. This review highlights the main landmarks in this journey and serves as a reminder of the importance of taking the "long view" when working toward international standardization. It demonstrates the need for continual maintenance and enhancement of standards to meet the changing needs of the cell therapy industry and highlights recent developments in ISBT 128.

Introduction

The identification and labeling landscape was very diverse prior to the launch of the standardization initiative. Cellular therapy products, primarily hematopoietic progenitor cells (HPCs), were identified in a variety of ways, including via the use of hospital identification numbers, patient names and dates of birth and national person identifiers [1]. The degree of uniqueness depended on the identifier. Name and date of birth are not guaranteed to be unique in any setting, hospital identifiers are unique within the hospital but may duplicate identifiers used by other hospitals and national identifiers are unique within the country but are not unique internationally.

Labels were frequently handwritten, and risks associated with spelling or numerical transposition errors could not be easily identified or mitigated. Poor legibility and inconsistencies in the information provided were also of concern (Figure 1). Matched allogeneic donor products, both related and unrelated, were described on accompanying paper records that sometimes lacked essential information.

With the formation of Bone Marrow Donors Worldwide in 1989 [2], the challenges of product labeling quickly became apparent. Products were described on the labels in the national language of the collection center using national terminology. With subsequent growth in the number of donor registries around the world, international distribution of cellular therapy products increased (Figure 2) [3]. The problem was exacerbated by product labels from one country being very difficult to read in another.

The Pioneers

The first facilities were registered to use ISBT 128 for HPCs in 1996, and in 1997 the Carolinas Cord Blood Bank issued HPC products labeled using ISBT 128 terminology. In Sweden, the move toward ISBT 128 for cellular therapy products commenced in the late1990s. At that time, HPC collection and processing were mainly performed at blood centers, requiring standardized product coding similar to that used for blood components using the same computer system. The need for coordination of product coding was recognized. A diverse work group from the different regions was formed with the

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HPC, Apheresis
Mobilized
Unrelated Donor
For Use by Intended Recipient Only
Donor ID 165-7527-7
Recipient ID 745-698-2
Intended Recipient: Duck, Donald
Collection Date: 25 MAR 2010 (DD/MMM/YYYY)
Collection End Time 0406 (24 hour clock) Time Zone: CDT
Anticoagulant: ACD Volume: 42 mL
Heparin Vial Concentration: AA units/mL Volume: AA mL
Concurrently Collected Plasma Present, Added After Collection ☐
Other Additives: ☐ See Attached Documentation for Details
Total Volume: 280 mL
Store At: 1-10 C
Infuse Within 48 hours of Collection or as Soon as Feasible
Caution: New Drug-Limited by United States Law to Investigational Use
Warnings:
Do Not Irradiate
Do Not Use Leukoreduction Filters
L00001 Rev. 4

Figure 1. Example of handwritten label with poor legibility.

Figure 3. ISBT 128 label used in Sweden in 2009.

main purpose of coordinating and translating codes in a uniform way. HPC processing was added, and group members worked together to define the necessary component codes. From 2006 on, the ISBT 128 coding system was gradually introduced for the coding of HPCs and other cellular therapies (Figure 3).

Labeling Challenges

Concerns over the quality of cellular therapy products and their identification led to the development of professional standards and regulation in many countries and regions. Examples include the accreditation standards of the Association for the Advancement of Blood and Biotherapies (AABB) and Foundation for the Accreditation of Cellular Therapy (FACT)/Joint Accreditation Committee of the International Society for Cell & Gene Therapy (ISCT) and European Society for Blood and Marrow Transplantation (EBMT) (JACIE) as well as European Union Directive 2004/23/EC and the US Food and Drug Administration's regulation of human cells, tissues and cellular- and tissue-based products.

By the early 2000s, regulation and accreditation standards included requirements to control labeling quality and processes. However, the diversity of languages and terminology was not addressed at that time. Labeling compliance was a major challenge for cell therapy facilities. Labels were based on blank templates that were completed by hand. Instructions on required information were often lacking, and standard operating procedures either did not exist or had insufficient detail on labeling requirements. As a result, labels were often inadequately completed. The lack of formal label systems meant that statistics on label errors were not maintained, and therefore the scope of the problem was not well recognized at the time. Inspections by accreditation bodies began to identify this as a major contributor to non-conformances (Figure 4) [4,5]. Between 2004 and 2007, 16% of non-conformances found during JACIE inspections were due to label deficiencies. Developments in cellular therapies led to a greater variety of products and a corresponding greater need for more detailed information on the cellular product itself as well as anticoagulants, media and storage conditions.

International Collaboration

It was against this background that a meeting was held during the EBMT conference in Prague in 2005 between representatives from AABB, FACT, JACIE and the International Council for Commonality in Blood Banking Automation (ICCBBA) to consider whether use of the ISBT 128 Standard—already growing in use in blood transfusion—could be systematically applied to cell therapy. The benefit of globally unique identification and international standardization of

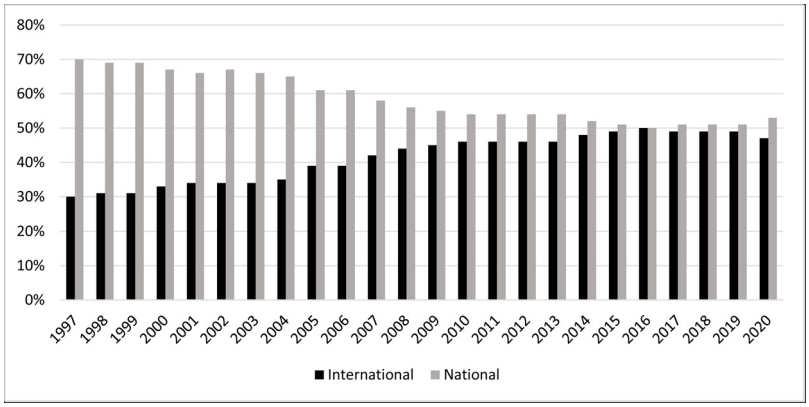

Figure 2. Percentage of HPC product shipments provided for international and national patients by year based on WMDA Global Trends Report 2020. WMDA, World Marrow Donor Association.

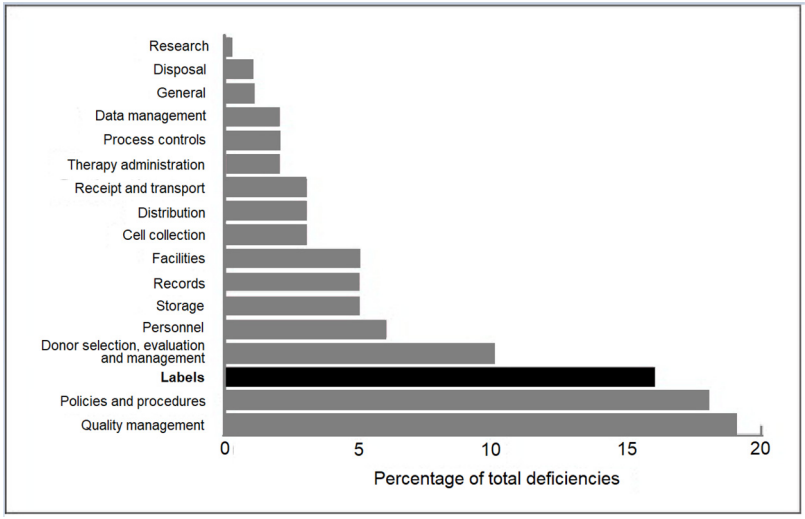

Figure 4. Deficiencies by category in JACIE inspections conducted from 2004 to 2007, as documented by Pamphilon *et al.* [5].

terminology with supporting coding and labeling was recognized. It was agreed that the best approach would be to form an international advisory group with representation from major cell therapy professional organizations to develop and manage a standardized cell therapy terminology and labeling standard. This proposal was presented at the ISCT Annual Meeting in 2005 and received strong support.

The first meeting of the Cellular Therapy Coding and Labeling Advisory Group (CTCLAG) was held in September 2005 in Athens, Greece, with representatives from AABB, EBMT, FACT, ICCBBA, ISCT, JACIE and the World Marrow Donor Association (WMDA). The American Society for Blood and Marrow Transplantation (ASBMT) and National Marrow Donor Program (NMDP) were involved from the outset but were unable to participate in the inaugural meeting. The work plan included standardization of product terminology, mapping of existing products to this terminology, label design, development of a mechanism for new terminology and code requests and global promotion of the standardization initiative.

To raise awareness of the work and wide professional commitment to standardization, a consensus statement was endorsed by the boards of AABB, the American Society for Blood and Marrow Transplantation, the American Society for Apheresis, EBMT, FACT, ICCBBA, the International Society of Blood Transfusion, ISCT, ISCT Europe, JACIE, NMDP and the World Marrow Donor Association. The statement confirmed support for the international use of ISBT 128 in the coding of HPCs and other cellular therapy products. It also announced the formation of the co-sponsored international CTCLAG to (i) review existing regulation regarding labeling, (ii) design product label templates that satisfy regulatory requirements, (iii) provide a focus for the standardization of terminology and product naming, (iv) promote adoption of the ISBT 128 Standard in cellular therapy facilities around the world, (v) provide advice and support to facilities introducing the standard and (vi) advise on the ongoing development of the ISBT 128 Standard to support new developments in cellular therapy.

Initially, the primary efforts of CTCLAG were divided into two work groups: terminology and label design. The members met by conference call and face-to-face meetings associated with meetings of the endorsing professional societies. The original terminology was developed for HPCs using class, modifier and attribute following the coding approach used for blood products. Draft label content and design included product identification information for both a full-face label and a partial label. The first label template for cellular therapy products debuted at the ISCT meeting in May 2006. Six months later, CTCLAG met to establish timelines for completing terminology and finalizing label content and design.

The standardized terminology was developed by CTCLAG and released for public consultation in January 2007. The final terminology was published in 2007 concurrently in three peer-reviewed journals along with an accompanying article on developing an ISBT 128 implementation plan for cellular therapy facilities [6,7]. Through the years, CTCLAG, endorsing professional societies, accreditation organizations and ICCBBA staff have provided many educational sessions and resources on ISBT 128 terminology, data structure, product description codes, label design and labeling standard implementation.

The ISBT 128 terminology continued to expand, and the consensus statement was updated in 2011 to recognize the growing use of non-HPC products. It was necessary to reevaluate some of the terminology and modify the coding approach. The term “therapeutic cell” as a class of product was retired. There was concern that use of this term would imply a proven therapeutic product. In 2013, the terminology was revised to reflect a new class structure and eliminate modifiers from the coding hierarchy. Modifiers were moved into an expanded attribute group to allow growth within the database structure and align with emerging tissue product terminology and coding.

Accreditation Standards: an Incremental Approach

Accrediting organizations recognized the impact of requiring implementation of ISBT 128 on cellular therapy facilities. In 2010, the endorsing organizations solicited information with “ISBT 128 labeling for cellular therapy products: an international survey” to identify roadblocks to implementation. The accrediting organizations used this information to help end users identify needed support and infrastructure and develop timelines for full adoption and implementation of the labeling standard. The accreditation standards of AABB and FACT/JACIE adopted an incremental approach to the implementation of ISBT 128.

ISBT 128 nomenclature was introduced into the *Circular of Information for the Use of Cellular Therapy Products* and subsequently made an accreditation requirement in the third editions of the AABB Standards for Cellular Therapy Services and the FACT/JACIE International Standards for Hematopoietic Cellular Therapy (2006). In the fifth editions, both standards required facilities to have an implementation plan for ISBT 128. The subsequent requirements for ISBT 128 implementation included the use of scanned information at the time of product release from collection, upon receipt in the laboratory and

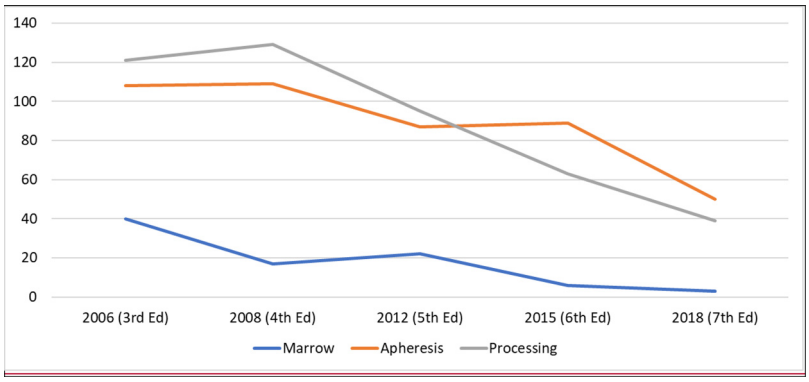

Figure 5. Number of FACT labeling citations by edition of standard. (Color version of figure is available online.)

at distribution from the processing facility. For facilities being inspected soon after the effective date of the sixth version, minimal criteria were identified to show that the facility was "actively implementing" ISBT 128. In the eighth edition of the AABB Standards for Cellular Therapy Services, accredited facilities were required to be in compliance with ISBT 128 labels for their labeling by July 1, 2018.

Citations for labeling non-conformance have dropped steadily as these requirements have been introduced. FACT recorded 269 citations associated with labeling against the third edition standard, but by the seventh edition, this had fallen to 92 (Figure 5). AABB has seen a similar reduction in citations associated with labeling (seventh edition, n = 19, eighth edition, n = 10, ninth edition, n = 5, 10th edition, n = 2 to date). Today, both the AABB Standards for Cellular Therapy Services and FACT/JACIE International Standards for Hematopoietic Cellular Therapy require the use of ISBT 128 nomenclature and full implementation of coding and labeling according to international standards.

National and Regional Initiatives

In 2011, NMDP/Be The Match identified the benefits of a national approach to standardization of coding and labeling. NMDP understood that implementing a change of this magnitude would require enormous effort and could be burdensome to individual centers, potentially leading to a failed initiative. The solution included a team approach with education and the provision of resources to individual centers. The goal of this project was greater safety, accuracy and efficiency in cellular therapy service delivery.

The NMDP team proceeded with assessment, analysis and planning phases as well as collection site visits. Collection centers reported a lack of resources and funding available to support the project on a site-by-site basis. NMDP adopted a centralized approach to procurement of a labeling solution and provided resources to most of the larger collection centers to help them move forward. A software and labeling vendor was selected, and an implementation package was developed that included the stand-alone HemaTrax-CT ISBT 128 labeling system (Digi-Trax, Lincolnshire, IL, USA), validation, approval and management tools as well as labeling procedures, training modules and a support service.

Implementation for NMDP collection centers commenced in 2014 with staggered implementation through December 2016. Throughout this period, dual labeling systems using both manual methods and ISBT 128 were in place for NMDP products. In January 2017, ISBT 128 product labeling was required for all NMDP products collected in the US. NMDP support was critical in achieving the success of this project, as it allowed individual centers to implement the complex system with available resources and helped to expedite this important patient safety-related improvement.

In Europe, Directive 2004/23/EC required that Member States ensure the traceability of human tissues and cells from the donor to the recipient and vice versa. The European Commission was developing regulations to require a standard code. The Single European Code would apply to all tissue and cell products. ICCBBA participated in the work groups developing this code and ensured compatibility between ISBT 128 and the Single European Code. In 2015, a formal agreement was signed between the European Commission and ICCBBA, and ISBT 128 product description codes were included in the European Union Tissue and Cell Product Compendium. ISBT 128 was recognized as a permitted coding system in Commission Directive 2015/565. Figure 6 shows the major milestones in this journey toward standardization.

Current Status

The adoption of ISBT 128 for cellular therapy products is increasing steadily worldwide. Figure 7 shows the trend of increasing facility registration. Currently, approximately 60 new facilities register each year, and by 2021, there were more than 1000 registered cellular therapy facilities in 66 countries. ISBT 128 terminology for cellular therapy is updated and maintained under the

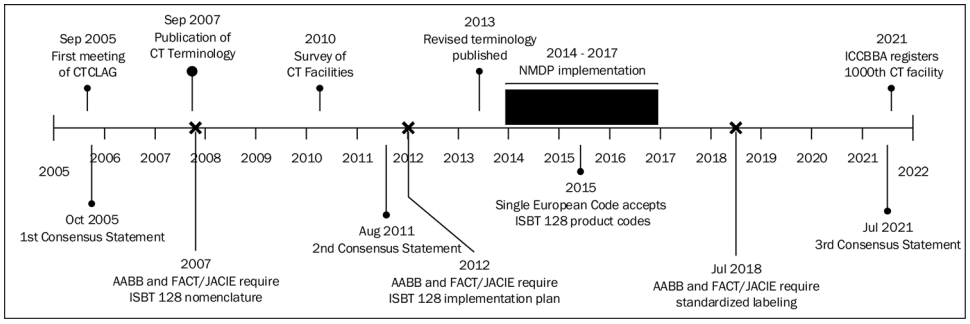

Figure 6. Standardization timeline.

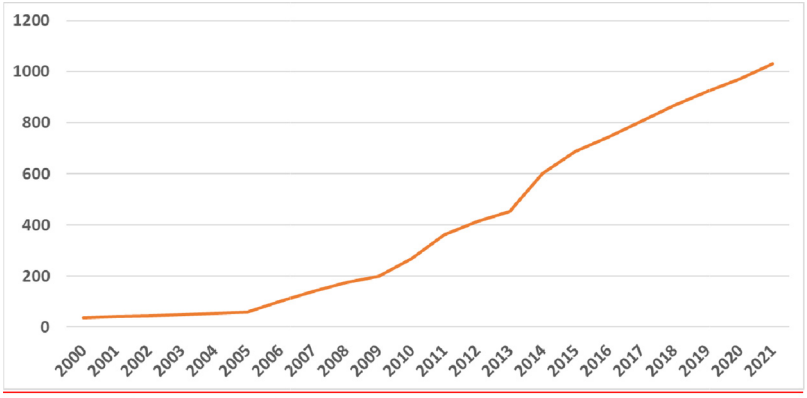

Figure 7. Number of cellular therapy facilities worldwide registered to use ISBT 128. (Color version of figure is available online.)

guidance of CTCLAG to reflect rapidly developing industry needs. Each year, two to three new classes are added to the terminology, and almost 200 new product description codes are added to the product database. ISBT 128 product terminology has been widely adopted, and ICCBBA and ISCT recently worked jointly on a statement on standard nomenclature for the tissue of origin of mesenchymal stromal cells [8].

Recent Developments

New developments support the use of ISBT 128 for cellular therapy in clinical trials and further manufacture. In collaboration with the Standards Coordinating Body for Regenerative Medicine and a broad spectrum of industry partners, accrediting associations and subject matter experts, ICCBBA developed an innovative split-label design for cellular therapy products for further manufacture, capturing ISBT 128 traceability information on one side and providing space for information specific to clinical trial/manufactured products on the other. In 2020, a new standard, ST-018 Labeling of Collection Products for Cellular Therapy Manufacturing, was launched, with additional guidance provided in IG-045 Applying ISBT 128 Labels to Collection Products for Further Manufacture.

To provide a mechanism for ISBT 128 labeling of cellular therapy products that have an International Nonproprietary Name (INN), ST-016 ISBT 128 Standard Labeling of Medical Products of Human Origin with INN and USAN Nonproprietary Names was developed in 2018. The standard describes the process for manufacturers to request an ISBT 128 product description code specific to an INN.

Where products are still in clinical trials, it may not be appropriate to assign an internationally standardized product description code, but the need for a product description code unique to the product remains. ICCBBA has thus developed a mechanism to allow clinical trial sponsors to be assigned a range of product description codes for their own use. These codes are not associated with international terminology but are linked to the sponsor, allowing the sponsor to assign their own product description during the clinical trial.

These developments provide a consistent standardized approach to labeling cellular therapy products for human use and facilitate traceability and biovigilance. The importance of standardized terminology, coding and labeling was reinforced in July 2021 with the release of an updated consensus statement, endorsed by many professional societies and accreditation bodies, on the use of ISBT 128 for cellular therapy [9]. CTCLAG continues to ensure that the ISBT 128 Standard remains relevant and fit for purpose.

Discussion

Building consensus and implementing standards at the international level required considerable effort over many years. However, the benefits of standardization have been substantial. Accreditation bodies have seen a steady reduction in citations associated with labeling deficiencies, indicating an improvement in labeling quality and recipient safety. The widespread implementation of ISBT 128 in cellular therapy has facilitated international movement of products, enhanced traceability and improved the accuracy and reliability of information on product labels. As the use of ISBT 128 has grown, the confidence of stakeholders has also increased. This enables the development process to be expedited.

The voluntary contribution of time and expertise by a wide range of experts and the commitment of professional societies have been critical to this progress. The needs of the cellular therapy community will continue to change over time, and the ISBT 128 Standard will continue to evolve to meet these needs.

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Author Contributions

Conception and design of the study: PA . Acquisition of data: PA, SA, SL, KL, KM, LSP, ISC, ZS. Analysis and interpretation of data: PA, SA, SL, KL, KM, LSP, ISC, ZS. Drafting or revising the manuscript: PA, SA, SL, KL, KM, LSP, ISC, ZS. All authors have approved the final article.

Declaration of Competing Interest

The authors have no commercial, proprietary or financial interest in the products or companies described in this article.

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