World Marrow Donor Association	Introduction and Importance of a Globally Unique Identity and Labeling Format (ISBT 128)			
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Introduction and Importance of a Globally Unique Identity and Labeling Format (*ISBT 128*)

Cellular therapy (CT) started with stem cell transplantation using bone marrow as a source of hematopoietic progenitor cells (HPC, Bone Marrow) in the early 1980s. This field has been rapidly expanding in the last two decades, because other sources such as mobilized progenitor cells harvested by apheresis machines (HPC, Apheresis) and HPC from cord blood (HPC, Cord Blood) have proved to be excellent sources of HPCs for stem cell transplantation. Since then, the treatment of patients with matched unrelated donor transplants has improved considerably and now a worldwide exchange of CT-products has become evident.[2] The World Marrow Donor Association (WMDA) published their data on export and import, showing that nearly 50% of the HPC products for matched unrelated donor transplantation are exchanged internationally (WMDA 2009 Annual Report[1]). Effective traceability and biovigilance in the global context depends upon the use of globally unique identification for all donated biologic products, including cellular therapy products today and in the future.

ISBT 128 is an identity and coding system that meets those basic requirements from a global perspective. This system was originally developed to improve the safety, quality and traceability of blood and blood components by the International Society of Blood Transfusion (ISBT). It was launched at the meeting of the ISBT in Amsterdam in 1994 and since then, the system has been integrated in blood banks all over the world. Today the standard is managed by ICCBBA[2-7].

Specific industry-wide benefits of *ISBT 128* adaption for cellular therapy would include:

- Globally unique identity which supports traceability of product from donor to recipient and recipient to donor and is not compromised by transcription errors or mix-ups that can occur during product relabeling
- Globally unique identity prevents duplication of numbers, especially in environment where transplantation products are received from multiple facilities worldwide
- Commonality of labeling format, product identity and descriptions with standard data structure supports computer assisted technology and ability to bar code information to limit error and transmit critical product information across language barriers using cost-efficient automated technology
- A common label format supports identity verification and safe infusion of the right product to the right patient across language barriers
- International standardization of product identity and labeling information supports the ability to share data electronically and monitor adverse events and reactions or biovigilance initiatives effectively.

The WMDA Board supports the initiatives of ICCBBA in relation to the use of *ISBT 128* for cellular therapy products. This paper provides information about the position of the WMDA regarding the ISBT product identity and coding system and the regulatory landscape on coding and labeling.

WMDA and Support of *ISBT 128*

WMDA has been actively involved in an international technical advisory group to International Council for Commonality in Blood Banking Automation, Inc**,** (ICCBBA) called the Cellular Therapy Coding and Labeling Advisory Group, (CTCLAG), since this advisory group was established in 2004. Together with technical experts and regulatory representatives from various settings, this group advises ICCBBA and works together to develop standardized international coding and labeling for new products and works to support global harmonization. Membership comprises representatives from major cellular therapy professional organizations: AABB, Asia Pacific Blood and Marrow Transplantation (APBMT), American Society for Blood and Marrow Transplantation (ASBMT), American Society for Apheresis (ASFA), European Group for Blood and Marrow Transplantation (EBMT), Foundation for the Accreditation of Cellular Therapy (FACT), The International Council for Commonality in Blood Banking Automation (ICCBBA), International Society for Blood Transfusion (ISBT), The Japan Society for Hematopoietic Cell Transplantation (JHSCT), Joint Accreditation Committee –ISCT and EBMT (JACIE), National Marrow Donor Program (NMDP) and World Marrow Donor Association (WMDA).

In 2005, the WMDA Board was one of many cellular therapy professional organizations to approve a consensus statement to recognize the benefits of the *ISBT 128* coding system as an information standard used to describe, name and label cellular therapy products internationally, as well as provide a mechanism to support a globally unique numbering system for cellular therapy products. In October 2010, the WMDA Board approved the Second Consensus Statement on Terminology, Coding and Labeling of Cellular Therapy Products which:

- Acknowledges the progress that has been made by the CTCLAG
- Encourages the implementation of *ISBT 128* coding and labeling system to support global standardization and encourages other industry organizations to support this effort
- Requests the CTCLAG to address terminology for non-hematopoietic cellular therapy products

As *ISBT 128* terminology is currently required by the Standards of AABB, FACT and JACIE and is included in the Circular of Information, an increasing number of facilities are using this terminology and beginning to fully implement *ISBT 128*, including label design and bar codes. WMDA encourages the efforts to adapt *ISBT 128* as an effective bar-coded information coding system that supports a globally unique identity, standardized product coding and full traceability of cellular therapy products.

Regulations for Coding and Labeling and International Support

Regulatory bodies and professional cellular therapy organizations worldwide recognize the benefit and criticality of a globally unique numbering system that supports full traceability of cellular therapy products from the donor to the patient worldwide. Efforts

towards adaption of *ISBT 128* as an acceptable coding system for product identity, specific to national competent authority/requirements are in progress.

During the 63rd World Health Assembly held in Geneva, Switzerland from May 17-21, 2010, coding and traceability of cells, tissues and organs was discussed, including the use of *ISBT 128* as a solution for ensuring worldwide traceability for transplantation products. As an outcome of that discussion, a resolution was passed to reaffirm the guiding principles of the World Health Organization adopted in May 2008 which require implementation of quality systems including traceability, both nationally and for exported human products while ensuring that personal anonymity and privacy of donors and recipients are protected. The resolution supports implementation of systems to support traceability for cellular therapy products, specifically stating "Internationally agreed means of coding to identify tissues and cells used in transplantation are essential for full traceability[8-9].

Recently in the United States, the FDA released a final guidance document in March, 2010, "Guidance for Industry Standards for Securing the Drug Supply Chain - Standardized Numerical Identification for Prescription Drug Packages[10]." This document recognizes *ISBT 128* as an effective standardized numerical identification (SNI) system and effective technology for cellular therapy products subject to this requirement as a drug product. A robust system of uniqueness and traceability, as well as a method for eye-readable and machine-readable information is inherent in the acknowledgement of *ISBT 128* as a recognized numbering and information standard and an acceptable SNI for use with cellular therapy products per this guidance document.

The requirement exists within the European Union for the development and adaption of a single European Coding System for the traceability and coding of information about the main characteristics and properties of tissues and cells (Directive 2004/23/EC[11] and Commission Directive 2006/86/EC[12]). As in the U.S., *ISBT 128* has been proposed as a globally unique donation product numbering and information coding system that meets these EU requirements. *ISBT 128* was recommended to be used as the basis for meeting this EU requirement by the European Committee for Standardization (CEN)/ Information Society Standardization System (ISSS) Workshop. Under the auspices of the European Commission, a summary report for the 1ST Joint Meeting of the Competent Authorities and the Regulatory Committee on Tissues and Cells held on May 20-21, 2010, reiterates the needs for a robust single system for global traceability and coding for cellular therapy products and reported on progress to date. The system must also be consistent with laws of individual countries regarding product identity and confidentiality. To date, no decision has been made by the European Commission regarding the acceptance of *ISBT 128* as an approved approach to meeting these requirements. A decision to accept the use of *ISBT 128* would support the guiding principles of the World Health Organization adopted in May 2008 that requires implementation of quality systems including traceability, both nationally and for exported human products.

There are similar requirements for both confidentiality and traceability in many countries worldwide. Although similar regulatory discussions regarding specific coding and labeling regulatory standards may not have occurred or are in preliminary stages based on information obtained from WMDA Regulatory and Legal Affairs Committee members and others, *ISBT 128* is a method to accomplish both objectives. In addition, in some countries, following guidelines outlined by cellular therapy accrediting organizations may be required. In that context, the adoption of plans for and implementation of *ISBT 128* as a labeling system by these organizations will support adaption of *ISBT 128* as a global labeling standard.

Confidentiality and Identity of Facility/ Entity Perspective

In addition to robust traceability requirements, protecting the confidentiality of both the donor and the recipient is a cornerstone of the confidentiality requirements in the cell therapy industry. Although somewhat universal, specific confidentiality requirements and interpretation may vary from country to country.

A summary of the primary U.S. and European Commission confidentiality requirements and identity of the entity responsible for the cellular therapy product at distribution is provided below.

In the U.S., The Privacy Act, 5 US Code 552a[13], prohibits the disclosure of medical information containing confidential individually identifying information without written consent. Under the Transplant Amendment Act, US Code Title 42, a system of strict confidentiality to protect the identity of patients and donors, as well as a method to ensure traceability between a maternal donor and a cord blood unit is also required. 21 Code of Federal Regulations (CFR) 1271[14] requires a unique identifier to maintain traceability and the ability to trace donor to recipient and vice versa without the use of name, social security number or medical record number. The name and address of the establishment that determines the product is available for distribution is also required by 21-CFR-1271. For FDA-approved drug products, 21-CFR-201[15] requires the identity of establishments involved in manufacturing as part of the drug product label.

Similar to U.S. requirements, the European Commission Directives require that all necessary measures be taken to protect health-related information. A donor identification system for each donation is required to ensure a unique identity and label and support traceability at all times while protecting the anonymity of the donor and patient. The ability to track donor to recipient and vice versa is required. The identity of the tissue establishment at distribution is part of the label.

ISBT 128 Donation Identification Number (DIN) and Facility Identification Number (FIN)

The structure of the *ISBT 128* globally unique donation identification number has three distinct parts and is outlined in the table below. This 13 character numbering system is

bar code readable, includes a "checksum character" to effectively detect keyboard entry errors in computer systems (see Attachments A and B for examples of label format with unique donation identification format highlighted).

Basic Donation Identification Number (DIN) Structure

W0000	**09**	**123456**
ICCBBA assigned Facility Identification Number (FIN)	Two-Character Year of Collection	Facility-Assigned Serial Number

The Facility Identification Number (FIN) is a unique facility identity assigned by ICCBBA. The "FIN" can designate the collection site or the donor registry. In the case of cord blood collections, the cord blood bank that is administratively responsible for the collection may be the "FIN" identity. When taken together, the combination of all three parts of the Donation Identification Number (DIN) is what makes the 13-character *ISBT 128* numbering system a globally unique number. If any of the parts of the Donation Identification Number (DIN) is obliterated, covered up or shortened (the FIN, Year or Serial Number), the integrity of the globally unique number is compromised.

When this "FIN" information is included as part of a product label, the standardized *ISBT 128* label format is designed to contain the identity of the facility that corresponds to the "FIN" in both eye-readable format as part of the product label and in bar-coded format as part of the product identity. Although the collection facility is not considered part of personal health information in the U.S. and many other countries with regard to protecting donor confidentiality, the label can also be configured so that the eye-readable identity of the facility corresponding to the "FIN" is not displayed on the label. This approach is applicable in the setting of unrelated, allogeneic donor collection in many countries and would meet international requirements for robust traceability, as well as the confidentiality as cited above. In this way, the 13 characters globally unique number is not compromised, while still assuring that the identity of the collection facility is not "eye-readable" as part of the attached label.

The *ISBT 128* label format listing the collection site is consistent with the U.S. label requirements defined in 21 CFR 1271 at distribution and with those defined in 21 CFR 201 as part of drug manufacturing, as described above. The *ISBT 128-label* format is also consistent with the European requirement defined in 2004/23/EC for the label at distribution to include the identification of the tissue establishment. As noted in earlier report, it supports the WHO guidelines for traceability for cellular therapy products worldwide (see label upper left quadrant of label examples; Attachment A showing an unrelated donor setting where the facility corresponding to the "FIN" is not eye-readable and Attachment B for a related donor setting where the facility corresponding to the "FIN" can be designed to include this information in eye-readable format).

Labeling Options for "FIN" Assignment

For some time, the international cellular therapy community has been discussing various options for designating the entity assigned as the "FIN" within the unique global Donation Identification Number (DIN) as the collection facility, tissue establishment or the registry in context of adult stem cell donors and international regulatory requirements. These discussions have focused on the requirements to ensure a robust traceability system while protecting the confidentiality of the patient and donor, especially in the context of the facility/ organization identified in the "FIN". Because the identified "FIN" facility/organization does not appear on the final attached label in eye-readable format, it is possible to use a "look-up" tool on the ICCBBA website to identify that facility assigned to the "FIN". This supports the labeling regulatory requirements for the distribution label outlined above, while still protecting the personal identifying information of the donor. A summary of the major "FIN" assignment options, with comments are presented below.

Collection Facility identified as the "FIN" identity within the "DIN"; assigned by ICCBBA

Collection Facility (or tissue establishment) is identified on the label in machine-readable format only for allogeneic donations. In this setting, the identity of the collection facility or tissue establishment required as part of the labeling regulatory requirements is contained in the accompanying labeling documentation "paperwork" for the unit and is not part of the attached label in "eye-readable" format to support confidentiality requirements of some countries.

Comments about benefit and risk:

- Standard format as originally defined and controlled centrally by ICCBBA.
- When the collection facility controls their own labels and the collection site is defined on the label as the "FIN", one DIN can be used by the collection facility for autologous, related and unrelated product.
- One DIN for all products is simplest, most cost effective approach for manual and automated label control, validation, etc.
- Supports full traceability from collection to bedside with minimized risk for labeling errors because one DIN is in use for all products from that collection site.
- Supports requirements for tissue establishment to be identified on distribution label per EU requirements and the entity responsible for release (and manufacturing, where applicable) per U.S. requirements.

Collection Facility identified as the "FIN" identity within the "DIN"; assigned by Registry

Collection facility (or tissue establishment) is identified on the label in machine-readable format only for allogeneic donations. In this setting, the identity of the collection facility or tissue establishment required as part of the labeling regulatory requirements is contained in the accompanying labeling documentation "paperwork" for

the unit and is not part of the attached label in “eye-readable” format to support confidentiality requirements of some countries.

Comments about benefit and risk:

- ICCBBA no longer controls the assignment of “FIN” to collection facilities; decentralized control at registries worldwide increases opportunity for “FIN” assignment error and compromises traceability and globally unique numbering system (Errors and duplication of numbering systems have occurred historically in current decentralized systems).
- This model necessitates a different DIN numbering system for registry (allogeneic unrelated) vs. non-registry (autologous and related) products, with increased complexity and opportunity for error.
- When the “FIN” is controlled and assigned by each registry per this model, the varied cooperative and multiple registry relationships across the world could result in several different DIN numbering systems in place to accommodate the multiple registries a collection facility may work with.
- This model complicates the labeling processes/control with increased confusion and chance for errors that affect global uniqueness of numbering, labeling mix-ups and traceability.
- This model requires complex label control of automated or manual labeling and increased validation complexity for computerized labeling systems
- This model results in increased administrative burden and cost for registry; especially larger registries with multiple collection relationships and numbering systems to manage.

Registry identified as the “FIN” identity within the “DIN”

The Registry, rather than the collection facility or tissue establishment is identified on the label in machine-readable format and eye readable format, if needed. In this setting, the Registry must maintain a robust label control system to assign and manage a series of unique identification numbers to each collection site the registry works with. In addition, the identity of the collection facility or tissue establishment required as part of the regulatory labeling requirements is no longer part of the affixed product label.

Comments about benefits and risk:

- Although ICCBBA controls the assignment of “FIN” within the “DIN” to a Registry, the registry controls the actual assignment of the unique identity to the collection sites it works with by assigning a “block” of DINs to each site. This model increases opportunity for “serial number” assignment error and duplication and increases risk of compromised traceability (errors and duplication of numbering systems have occurred historically in current decentralized systems).
- This model necessitates a different DIN numbering system for registry (allogeneic unrelated) vs. non-registry (autologous and related) products.
- When the “FIN and serial number” is controlled and assigned for each registry per this model, the complex cooperative and multiple registry relationships

across the world could result in several different DIN numbering systems in place to accommodate the multiple registries a collection facility may work with.
- This model complicates the labeling processes/ control even further than the option above with increased confusion and chance for errors that affect global uniqueness of numbering, labeling mix-ups and traceability.
- This model requires complex label control and increased validation complexity for computerized labeling systems
- This model does not support the requirements to identify the tissue establishment on the distribution label per EU requirements or the entity responsible for release (and manufacturing, where applicable) per U.S. requirements.
- This model results in increased administrative burden and cost for the Registry; especially larger registries with multiple collection relationships and resulting numbering systems.

Relabeling, obliterating or overlabeling the FIN upon receipt at transplant center

Collection facility (or tissue establishment) is identified on the label in machine-readable format only for allogeneic donations.
- These models do not support maintaining the integrity of the globally unique numbering system of the DIN (FIN + year + serial number).
- These models complicate labeling processes at the transplant center and increase chance for labeling error.
- These models do not support full traceability of the DIN from the collection to bedside.

Conclusion and WMDA Proposal

To encourage the benefit and criticality of a globally unique numbering system, WMDA recognizes the *ISBT 128* labeling standard as one that supports full traceability of cellular therapy products from the donor to the patient bedside and the flexibility to protect confidential information as defined by current and future international regulations. WMDA supports the simplest, most efficient system of labeling and assignment of the Facility Identification Number ("FIN") that minimizes the chance of confusion, error, label-mix-up and loss of traceability in the labeling processes. As such, WMDA supports the adaption of the *ISBT 128* Donation Identification Number (DIN) format and assignment of the "FIN" as the collection center (or tissue establishment), with centralized control at ICCBBA, whenever feasible and when consistent with the requirements of the national competent authority governing the registry and collection sites. In settings where it may be desirable to limit the access of the patient or patient's family to the identity of the tissue establishment that is required to be on the distribution label (or manufacturer or entity responsible for release), WMDA recommends that a removable sleeve or other temporary mechanism be used to cover any identity information (eye-readable or not eye-readable format) that is considered to be health related personal information by a national competent authority.

This mechanism should be used at the bedside after appropriate patient and unit identity has been verified. In this way, the integrity of the unique global donation number is maintained and the traceability of the donor to the recipient and vice versa is maintained, as well as supporting the regulatory requirements for the identity of the tissue establishment or collection site to be part of the product label. In addition, this adaption will support the continuing increase of international exchange of stem cell products and support safety for our transplant patients.

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