Cell Therapy Liaison Meeting, January 4, 2007

Host Organization

International Society for Cellular Therapy
ISCT

Moderator: *Stephen J. Noga, MD, PhD*

8:00-8:15 – Call to Order and Introduction of agenda and meeting participants

- Review of Summary and Action Items from June 16, 2006 Meeting

IMPORTATION AND EXPORTATION OF CELL PRODUCTS

There are large numbers and types of HCT/Ps that are transported across international boundaries, and as described in FDA regulations (e.g. 21 CFR 1271) importation and exportation of these cell products must follow specific rules and guidelines. However, there are still many questions regarding Affirmation of Compliance, Foreign Establishment Registration, Notification of FDA prior to importation, the accompanying Summary of Records, and Labeling requirements for HCT/Ps. In addition, to what extent distinctions between products regulated solely under section 361 of the PHS Act (e.g. related donor peripheral blood stem cells) versus those regulated under section 351 (e.g. unrelated donor PBSC) affect the importation process remains unclear. Discussion will focus on addressing these issues and clarifying these distinctions.

8:15-9:35 – **Industry Presentations**

- 8:15-8:45 NMDP screening process for PBSC and cord blood donors of products imported into the US (*Fran Rabe*)
- 8:45-8:55 Importing/exporting "conventional" HCT/Ps (*Scott A. Brubaker, CTBS*)
- 8:55-9:15 Overview of regulations of the major exporting European countries (*Speaker TBD*)
- 9:15-9:25 How we handle non-NMDP products (*John McMannis, PhD; Shelly Heimfeld, PhD*)
- 9:25-9:35 Third Edition of FACT-NetCord Cord Blood Standards and Update on Accreditation of Sites Outside the US *(Phyllis Warkentin, MD)*
- 9:35-9:45 AABB Accreditation of Sites Outside the US *(Karen Shoos Lipton, JD)*
- 9:45-9:55 Requirement to implement the National Drug Code (NDC) system for licensed HCT/Ps, including imported products as presented in the recently released proposed rule: *Requirements for Foreign and Domestic Establishment Registration and Listing for Human Drugs,*

Including Drugs that are Regulated Under a Biologics License Application, and Animal Drugs (Docket No. 2005N-0403, August 29, 2006). *(Joseph L. Giglio, MS, MT(ASCP)SBB, CSQE(ASQ), CQA)*

9:55-10:45 – **Discussion**

10:45-11:00 – BREAK

HOMOLOGOUS USE WHITE PAPER

The Homologous Use Working Group and corresponding Advisory Group were formed by ISCT, in conjunction with other stakeholders, to address confusion about FDA's application of the definition for "*homologous use"* as found in 21 CFR 1271 to different types of cell-based therapies. The Working Group was assigned the task of creating a white paper to clearly identify industry concerns surrounding the regulatory definition for "*homologous use"* and to offer preliminary solutions. The Working and Advisory Groups intend this Homologous Use white paper to be a vehicle for communication to other member organizations and to the FDA CBER Office of Cell, Tissue and Gene Therapy.

Additionally, there will be discussion on how *"homologous use*" with cell products could be demonstrated (i.e. what animal model data or scientific evidence could be generated that clearly indicates the biological mechanism responsible for the clinical efficacy is an inherent, well-understood property of the cells).

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11:45-11:55 – **Future Meetings**

- Identification of date, topics, format, etc. for next meetings

11:55-12:00 – **Conclusion** *(Stephen Noga, MD, PhD)*

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(Those shaded in grey did not attend)

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American Society for Apheresis (ASFA)

American Society for Blood and Marrow Transplantation (ASBMT)

American Society of Gene Therapy (ASGT)

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MEETING SUMMARY

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IMPORTATION AND EXPORTATION OF CELL PORDUCTS

Presentation by Phil Brown

Mr. Phil Brown, Quintiles Consulting, presented an overview of regulations of the major exporting European countries (see presentation 1).

Current Situation (January, 2007)

Phil Brown noted that there are two regulatory platforms in Europe: one for medical devices and one for medicinal products, with the difference being in the "primary mode of action" of the product, and its "intended purpose". Tissue Engineering, Cell Therapy, gene therapy, biotech products will generally fall under the pharmaceutical regulations however. With medical devices, the manufacturer most often meets a set of standards in order to satisfy a prescriptive set of "Essential Requirements", after which he can affix a CE Mark for sales and marketing throughout the European Union. Medicinal products are regulated and approved by EMEA (European Medicines Agency) and Committee for Proprietary Medicinal Products (CPMP). As it is difficult to pin down the mode of action of cells and tissues (regardless of viability), the regulation of these products is usually deferred to the national level:

- Ireland, Germany, Norway, Sweden, and Portugal generally consider tissue or cell products as pharmaceutical products
- UK, Netherlands, and Denmark recognize that there are not pan-European regulations
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Ultimately, manufacturers are facing different regulations in different countries (there are inconsistencies across both geographic and scientific platforms). As a result, there are even local hot-spots for regulations and investment as is seen in Germany, where individual cities or provinces have their own regulations.

Situation During 2007

"Procurement Directive" – Tissue/Cell Directive (2004/23/EC)

This Directive was developed and published by the DG (Direcorate Generale) SANCO as an umbrella directive, that has now been sub-divided for further clarification to;

- Donation, procurement, and testing of human tissues and cells (2006/17/EC)
- Processing, preservation, storage and distribution of human tissues & cells (2006/86/EC)

If a hospital deals with whole organs or tissues, it needs to follow all of 2004/23/EC. The 2004/23 was to be put in place by April 2006, with a grace period. Very few countries have adopted the 2004/23 into their own national regulations up until January 2007, but this is an ongoing process.

In any event, manufacturers of human tissue products must comply with 2006/17 and potentially the processing preservation etc., components 2006/86 if there are no other regulations to follow. It is likely that in the future however, a manufacturer will only be requested to follow 2006/17/EC, as those aspects of 2006/86/EC will be covered by the ATMP regulations or the medical device directive 93/42/EEC. Again however, consideration will need to be given to the "mode of action" and "intended purpose" of the product.

It is important to note however, that for manufacturers, in the absence of any other regulations, <u>all</u> of 2004/23/EC will apply.

ATMP Regulation (Post 2007)

ATMP regulation is the proposed legislation for human tissue products. There is however, still a potential gap between the this and the two other directives for medical devices and pharmaceuticals. Importantly the ATMP is for Medicinal Products, and therefore advanced therapies (tissue engineering, cell therapy, gene therapy) will be reviewed by a new review committee called the Committee for Advanced Therapies (CAT) within the EMEA.

Ongoing Discussion

The ATMP will cover tissue engineering through gene therapy products – anything from non-viable bone chips, skin products through to highly sophisticated gene therapy. However, the scope of the regulations is still in debate. Phil Brown noted that non-viable human products (human collagen etc.) are however, likely to be considered as a medical devices, with Anything that is viable being covered by the ATMP. The ATMP will be voted on at EU parliament at the end of April 2007.

ATMP would likely give exemptions to hospitals working with human tissue and supplying tissue at a local level and according to prescription.

Areas of ongoing discussion include:

- who should be within the CAT to ensure effective representation
- length of transition period (there is discussion of a two to four year grace period for existing product manufacturers
- how to deal with combination products

It is expect that a final document will be available by the end of 2007, with implementation in early 2008.

Questions

Dr. Celia Witten asked for specific examples of where cord blood might end up and where de-cellularized skin could end up. Phil Brown responded that blood products are regulated under a separate regulation. Medical device regulation would cover ancillary human products that enable devices. At the moment, de-cellularized skin would be considered a non-viable product, which would be regulated (or not) at the national level. Then nationally, it would be determined if the product is a medical device, a pharmaceutical etc. The actual donation, procurement and testing would fall under 2006/17.

Ms. Kathy Loper asked for and received clarification that umbilical cord blood would be falling under the blood product regulation.

Dr. Shelly Heimfeld asked how imported products would be handled. Phil Brown responded that presently product manufacturers in Europe all manufacture according to different guidelines (Germany uses GMP guidelines, UK uses Quality guidelines etc.). The US manufacturers would be facing some of the same issues that the Europeans do. Furthermore, a US company could export to the UK and then once the product is in Europe, it is relatively easy to distribute across Europe.

Dr. Scott Rowley asked if Phil Brown would address simple BMT products, specifically if there is regulation of bone marrow, cord blood or peripheral blood cells. Phil Brown noted that the new ATMP rules include some definitions of what constitutes manipulation of cell products. It is very similar to the rules for these products in the US (i.e. need to consider whether the product is being put on the market, whether the product is being manipulated etc.).

Presentation by Scott Brubaker, CTBS

Mr. Scott Brubaker, AATB, presented an overview of importing/exporting “conventional” HCT/Ps (see presentation 2).

Import of “Conventional” HCT/Ps

Scott Brubaker described “conventional” tissue banks (an FDA term from the preamble to the CGTP Final Rule used to describe the type of tissue bank that follows AATB Standards for Tissue Banking) as well as the types of “conventional” HCT/Ps. AATB standards that pertain to the import/export of “conventional” HCT/Ps were reviewed in detail. Scott Brubaker noted that the import of “conventional” HCT/Ps does not occur very often (for contract processing only; or for processing and distribution within the US or for export). Problems experienced at port of entry for imported HCT/Ps were described and specific examples were presented.

Export of Processed “Conventional” HCT/Ps

Scott Brubaker also discussed the export of processed “conventional” HCT/Ps, describing the types of tissues that are generally exported, noting that export occurs to approximately 40 countries. He stated that tissue types that are in short supply are not exported unless they are supplied for processing by that country. Again, problems experienced at the port of export were described and specific examples presented.

International Regulations in Development Re: Importation

Scott Brubaker discussed the various international regulations that are in development regarding the importation of HCT/Ps, specifically the European Union Commission Directive, Health Canada regulations, and UK regulations.

Presentation by Phyllis Warkentin, MD

Dr. Phyllis Warkentin, University of Nebraska Medical Center, presented an overview of the 3rd Edition of FACT-NetCord Cord Blood Standards and an update on accreditation of sites outside of the US (see presentation 3).

FACT/JACIE Standards

Dr. Warkentin noted that the 3rd Edition of the FACT-NetCord standards have been published in the last few months. She presented a history of both FACT and JACIE and listed the various countries that participate in JACIE. Currently, 151 sites are FACT accredited (US and Canada) and 34 sites are JACIE accredited (non-US).

FACT –JACIE international standards apply to hematopoietic progenitor cells from any tissue source and therapeutic cells (nucleated cells other than HPC). They cover all phases of collection, processing, administration (excluding collection and banking of cord blood cells) and require all clinical, collection and laboratory facilities to develop and maintain a comprehensive Quality Management Plan, evaluate and report outcomes, and comply with applicable laws.

The significant changes in the 3rd Edition are as follows:

- Restructured document to make sections parallel
- Expanded quality management throughout
- Regulatory requirements (FDA and EU)
- Redefined numbers requirements
- Expanded requirements for pediatric competencies
- Incorporate recommendation for ISBT128 terminology and labeling

NetCord-FACT Standards

The NetCord-FACT standards cover all phases of cord blood collection, processing, testing, banking, selection, and release. They require all cord blood banks (CBB) to maintain a comprehensive Quality Management Program, utilize validated methods, supplies, reagents, equipment, maintain product tracking, maintain details of clinical outcome, and comply with applicable laws. CBB must have a process to address every standard.

The significant changes in the 3rd Edition are as follows:

- Provisions for private (directed) banking
    - Most standards are identical – quality units required
    - Non-fixed collection sites
- Documented informed consent for collection (at least) required prior to collection
- Requirements in event of cessation of operations:
    - Maintain inventory, capacity to distribute
    - Document continued competency of staff prior to restart
    - Maintain contractual obligations with donor families
- Inclusion of QM/other standards to meet regulatory requirements – FDA, EU
- Clarify testing requirements
- CB unit storage temperature <-150C.

All FACT-NetCord accreditation takes place through the US-based Office. Currently 11 cord blood banks are FACT-NetCord accredited, with 4 of those being non-US based.

Applicable International Regulations

Dr. Warkentin described the applicable international regulations and discussed international accreditation issues such as:

- Language translation when CBB does not function in English:
- Testing for diseases uncommon in a specific country or that is not part of the routine for normal blood donors from that country.
- Labeling differences, particularly the use of the Biohazard label

Presentation by Karen Shoos-Lipton, JD

Ms. Karen Shoos-Lipton, CEO, AABB, presented an overview of AABB accreditation of sites outside of the US (see presentation 4). AABB has accredited 147 HPC and UCB facilities, with 17 outside the US

The AABB Standards Program

- Has a well defined infrastructure
- Process includes experts in the field, Ethicists, public, FDA and other orgs
- Has established timelines for updates
- Allows for interim and emergent standards
- Requires member and public comment period
- Standards developed in FDA regulated climate

The AABB Accreditation Program

- Well established program - 50 yrs.
- Designed to operate in a regulated climate
- Policies guide program
- Operates under internationally accepted standards for accrediting bodies
- Accreditation based on assessment of conformance to standards

The AABB international accreditation process is the same for all facilities with some international variances (applying to US specific details which other countries cannot meet such as testing) that are not routinely

granted.

Overall, AABB Standards comply with FDA GTPs and apply to imported products.

Karen Shoos-Lipton noted that the EU is also struggling with similar issues and that steps are being undertaken to address some of these. The Alliance for Harmonisation of Cellular Therapy Accreditation (AHCTA) is a multi-organizational group that has formed to begin work on this. The first project will be minimum import and export requirements.

Presentation by Fran Rabe

Fran Rabe, NMDP, provided an overview of the NMDP screening process for PBSC and cord blood donors of products imported into the US (see presentation 5).

US Importation of Peripheral Blood Stem Cells

In 2005, 390 units of PBSC were imported, with Germany being the primary source of these PBSCs. Fran Rabe discussed the NMDP donor screening requirements, which include a health history questionnaire, infectious disease testing and a physical exam. Details of each of these screening processes were presented. Screening is administered by the donor center/apheresis center.

US Importation of Cord Blood

In 2005, 21 units of cord blood were imported into the US. Factors that impact the screening process of cord blood donors are whether the collection of the cord blood occurred prior to or after 5/25/05 and whether the cord blood bank is an NMDP member or non-member. Different screening procedures apply based on these factors.

Presentation by John McMannis, PhD

Dr. John McMannis, MD Anderson Cancer Center presented an overview of unrelated products received from outside the NMDP structure (see presentation 6).

Dr. McMannis presented a snapshot of the current situation with unrelated transplants (developed by talking to directors from nine centers, including the top five centers based on NMDP numbers, doing a subset analysis of three of these centers, and providing a rough breakdown of numbers of products to point out trends). Ultimately, the majority come from NMDP sites, but the number coming from outside the US had been

increasing in each of the past 5 years and currently represents almost 25% of the products imported.

Furthermore the process that transplant centers use to qualify collection centers varies widely from center to center (and from product to product).

Some points to consider include:

- Do we need a better data set?
- Should there be minimum requirements for qualification of collection centers?
- Sliding scale based on clinical indication or basic minimum requirements?
- Use of FDA approved ID testing kits

Presentation by Joseph Giglio, MS, MT(ASCP) SBB, CSQE(ASQ), CQA

Mr. Joseph Giglio, AABB, presented an overview of requirement to implement the National Drug Code (NDC) system for licensed HCT/Ps including imported products as presented in the recently released rule: *Requirements for Foreign and Domestic Establishment Registration and Listing for Human Drugs, Including Drugs that are Regulated Under a Biologics License Application, and Animal Drugs* (Docket No. 2005N-0403, August 29, 2006) (see presentation 7).

Joseph Giglio noted that the NDC system is not a good fit for HPCs and TCs because:

- Biological nature/variable contents of HPCs and TCs
- HPCs and TCs are not mass-produced
- Overly burdensome with no increase to patient safety
- NDC number is not a useful reference in any federally maintained database -- products are infused/transplanted by the time the NDC number is available

Furthermore, there is a negative impact of implementing NDCs on HPCs and TCs:

- Current information systems cannot accommodate the NDC system
- Loss of standardization
- Multiple products and attributes of cellular products are not easily managed
- Overly burdensome and duplicative with no increase to patient safety

- Loss of confidentiality

Instead, there are benefits of using the ISBT 128 International Standard:

- Greater benefits and increase to patient safety than an NDC
- Globally unique product identifier
- Cellular Therapy Coding and Labeling Advisory Group (AABB, ASBMT, EBMT, FACT, ICCBBA, ISBT/ SITS, ISCT, ISCT Europe, JACIE, NMDP and WMDA)
- Industry familiarity with ISBT 128
- Excellent traceability/trackability of products
- Contains more information than the NDC code

Questions

Dr. Celia Witten asked about the current status of ISBT 128. Ms. Kathy Loper stated that documents have been finalized in their draft form, and will be posted on all the organizations websites next week (week of January 8th). The document is very international. The comment period will close on February 28th. The document will be published in May 2007 in time for the ISCT Annual Meeting, and will be published in Cytotherapy and Transfusion. Kathy Loper identified all the members of the Advisory Group and noted that at present, there is no Asian representation on the ISBT 128 Committee, but they are trying to make inroads there as well.

Dr. Phyllis Warkentin noted that not all centers have automated labeling systems. The ISBT 128 system will allow all centers to use the same terminology – but would not require that all have the same physical labeling system (some would be labeling manually, some would use automated computer systems).

FDA representatives provided clarification of the NDC issue. The proposed rule was published in August, 2006 and the comment period has been extended through the end of January, 2007. On December 11, 2006 there was a public meeting on the proposed rule. The FDA does not feel that the proposed rule is mutually exclusive of the ISBT 128.

Fran Rabe noted that we don't yet know what the licensure of these products would look like.

FDA representatives stated that the NDC preamble covers the intent – the need to know who is making the products.

Dr. Heimfeld asked the FDA if they have any comment on the import/export issues.

Representatives from the FDA asked why Germany is such a major source for the US in terms of import. Fran Rabe noted that Germany has the best established donor registry. Germany has a law where every citizen is registered with the government – the donors are easier to find, which has a huge impact on donor availability

Dr. McMannis (this might have been Fran, not John) noted that for NMDP about 11-12% of potential donors cannot be tracked down when they are matched – either they have moved or they become unwilling to donate.

Dr. Witten noted that when FDA is looking toward global harmonization, they are struggling with who their partners can or should be.

Kathy Loper suggested that the FDA should get in touch with the WMDA, adding that the German system for example, is known for requiring GMP. However, it is our understanding that there are nuances and loopholes in the system whereby the regulations do not apply to procedures involving such products if the entire collection, processing and infusion occur in a single operation or a single day.

Scott Brubaker noted that the EU Directive does not really include anything on import/export – and this will likely be the subject of a future directive.

HOMOLOGOUS USE WHITE PAPER

Presentation by Lizabeth Cardwell

Ms. Lizabeth Cardwell, Compliance Consulting, presented the work of the ISCT-developed Homologous Use Working Group (see presentation 8).

The Homologous Use Working Group and corresponding Advisory Group were formed by ISCT, in conjunction with other stakeholders, to address confusion about FDA's application of the definition for "*homologous use"* as found in 21 CFR 1271 to different types of cell-based therapies. The Working Group was assigned the task of creating a white paper to clearly identify industry concerns surrounding the regulatory definition for "*homologous use"* and to offer preliminary solutions. The Working and Advisory Groups intend this Homologous Use white paper to be a vehicle for communication to other member organizations and to the FDA CBER Office of Cell, Tissue and Gene Therapy.

Ultimately, the Homologous Use Working Group would like comment from the FDA and to publish the paper in Cytotherapy and/or other journals.

Presentation by Shelly Heimfeld, PhD

Experimental Evidence Demonstrating "Homologous Use"

For a history of the Homologous Use working group please see appendix 1.

Dr. Shelly Heimfeld presented an overview of how *"homologous use*" with cell products could be demonstrated (i.e. what animal model data or scientific evidence would need to be generated) (see presentation 9).

Discussion

1. Clarification of the Definition

21CFR1271.3

Homologous use: replacement or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic functions in the recipient as in the donor.

Proposal for consideration:

Homologous use: Intuitive or already clearly documented clinical evidence for efficacy in a specific clinical application. **It's not the product, it's the Clinical Application!**

2. Regulatory Options

Is there a way for an HCT/P to get off from the BLA track?

Proposal for consideration:

Homologous use: Intuitive or already clearly documented clinical evidence for efficacy in a specific clinical

application. **Once clinical data becomes available, product now "shifts" to meet the definition of 361**

Question for consideration: Should the Working Group be re-focused on data collection to demonstrate homologous vs. non-homologous?

A call for agenda items for the next meeting was put forth and attendees were asked to follow up with suggestions. It was decided that the next meeting would take place in June at the AABB National Office.

Appendix 1.

History of the Homologous Use Working Group

The consensus at the November 5, 2004 Cell Therapy Liaison Meeting held between the FDA and representatives of stakeholder organizations in cell therapy, was that **"a working group must be established to work on a guidance document for clarification of homologous use".**

ISCT announced establishment of the Working Group by distributing a notice inviting nominations for two positions:

(a) Expert working group – individuals who have a working knowledge of processing facilities and issues for a variety of cell types

(b) Broader advisory group – advise the expert working group by reviewing draft output and providing comment on select issues prior to seeking public comment

Nominations were to be done by the submission of a C.V. of the nominee to the ISCT Head Office no later than May 20, 2005. Self-nominations were accepted.

The Working Group's mandate was to:

(a) define and explain "*homologous use*" to the cellular therapy community

(b) simplify interpretation in a way that is equally applicable to all types of cells

(c) define scientific studies needed to assist with the definition

(d) identify potential critical path projects for FDA to assist in the definition

One of the primary goals of the Working Group was to draft a guidance document which attempts further clarification of "*homologous use*" for the cellular therapy community.

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It is important to note however, that for manufacturers, in the absence of any other regulations, <u>all</u> of 2004/23/EC will apply.

ATMP Regulation (Post 2007)

ATMP regulation is the proposed legislation for human tissue products. There is however, still a potential gap between the this and the two other directives for medical devices and pharmaceuticals. Importantly the ATMP is for Medicinal Products, and therefore advanced therapies (tissue engineering, cell therapy, gene therapy) will be reviewed by a new review committee called the Committee for Advanced Therapies (CAT) within the EMEA.

Ongoing Discussion

The ATMP will cover tissue engineering through gene therapy products – anything from non-viable bone chips, skin products through to highly sophisticated gene therapy. However, the scope of the regulations is still in debate. Phil Brown noted that non-viable human products (human collagen etc.) are however, likely to be considered as a medical devices, with Anything that is viable being covered by the ATMP. The ATMP will be voted on at EU parliament at the end of April 2007.

ATMP would likely give exemptions to hospitals working with human tissue and supplying tissue at a local level and according to prescription.

Areas of ongoing discussion include:

- who should be within the CAT to ensure effective representation

- length of transition period (there is discussion of a two to four year grace period for existing product manufacturers
- how to deal with combination products

It is expect that a final document will be available by the end of 2007, with implementation in early 2008.

Questions

Dr. Celia Witten asked for specific examples of where cord blood might end up and where de-cellularized skin could end up. Phil Brown responded that blood products are regulated under a separate regulation. Medical device regulation would cover ancillary human products that enable devices. At the moment, de-cellularized skin would be considered a non-viable product, which would be regulated (or not) at the national level. Then nationally, it would be determined if the product is a medical device, a pharmaceutical etc. The actual donation, procurement and testing would fall under 2006/17.

Ms. Kathy Loper asked for and received clarification that umbilical cord blood would be falling under the blood product regulation.

Dr. Shelly Heimfeld asked how imported products would be handled. Phil Brown responded that presently product manufacturers in Europe all manufacture according to different guidelines (Germany uses GMP guidelines, UK uses Quality guidelines etc.). The US manufacturers would be facing some of the same issues that the Europeans do. Furthermore, a US company could export to the UK and then once the product is in Europe, it is relatively easy to distribute across Europe.

Dr. Scott Rowley asked if Phil Brown would address simple BMT products, specifically if there is regulation of bone marrow, cord blood or peripheral blood cells. Phil Brown noted that the new ATMP rules include some definitions of what constitutes manipulation of cell products. It is very similar to the rules for these products in the US (i.e. need to consider whether the product is being put on the market, whether the product is being manipulated etc.).

Presentation by Scott Brubaker, CTBS

Mr. Scott Brubaker, AATB, presented an overview of importing/exporting “conventional” HCT/Ps (see presentation 2).

Import of “Conventional” HCT/Ps

Scott Brubaker described “conventional” tissue banks (an FDA term from the preamble to the CGTP Final Rule

used to describe the type of tissue bank that follows AATB Standards for Tissue Banking) as well as the types of "conventional" HCT/Ps. AATB standards that pertain to the import/export of "conventional" HCT/Ps were reviewed in detail. Scott Brubaker noted that the import of "conventional" HCT/Ps does not occur very often (for contract processing only; or for processing and distribution within the US or for export). Problems experienced at port of entry for imported HCT/Ps were described and specific examples were presented.

Export of Processed "Conventional" HCT/Ps

Scott Brubaker also discussed the export of processed "conventional" HCT/Ps, describing the types of tissues that are generally exported, noting that export occurs to approximately 40 countries. He stated that tissue types that are in short supply are not exported unless they are supplied for processing by that country. Again, problems experienced at the port of export were described and specific examples presented.

International Regulations in Development Re: Importation

Scott Brubaker discussed the various international regulations that are in development regarding the importation of HCT/Ps, specifically the European Union Commission Directive, Health Canada regulations, and UK regulations.

Presentation by Phyllis Warkentin, MD

Dr. Phyllis Warkentin, University of Nebraska Medical Center, presented an overview of the 3rd Edition of FACT-NetCord Cord Blood Standards and an update on accreditation of sites outside of the US (see presentation 3).

FACT/JACIE Standards

Dr. Warkentin noted that the 3rd Edition of the FACT-NetCord standards have been published in the last few months. She presented a history of both FACT and JACIE and listed the various countries that participate in JACIE. Currently, 151 sites are FACT accredited (US and Canada) and 34 sites are JACIE accredited (non-US).

FACT –JACIE international standards apply to hematopoietic progenitor cells from any tissue source and therapeutic cells (nucleated cells other than HPC). They cover all phases of collection, processing, administration (excluding collection and banking of cord blood cells) and require all clinical, collection and laboratory facilities to develop and maintain a comprehensive Quality Management Plan, evaluate and report outcomes, and comply with applicable laws.

The significant changes in the 3rd Edition are as follows:

- Restructured document to make sections parallel
- Expanded quality management throughout
- Regulatory requirements (FDA and EU)
- Redefined numbers requirements
- Expanded requirements for pediatric competencies
- Incorporate recommendation for ISBT128 terminology and labeling

NetCord-FACT Standards

The NetCord-FACT standards cover all phases of cord blood collection, processing, testing, banking, selection, and release. They require all cord blood banks (CBB) to maintain a comprehensive Quality Management Program, utilize validated methods, supplies, reagents, equipment, maintain product tracking, maintain details of clinical outcome, and comply with applicable laws. CBB must have a process to address every standard.

The significant changes in the 3rd Edition are as follows:

- Provisions for private (directed) banking
    - Most standards are identical – quality units required
    - Non-fixed collection sites
- Documented informed consent for collection (at least) required prior to collection
- Requirements in event of cessation of operations:
    - Maintain inventory, capacity to distribute
    - Document continued competency of staff prior to restart
    - Maintain contractual obligations with donor families
- Inclusion of QM/other standards to meet regulatory requirements – FDA, EU
- Clarify testing requirements
- CB unit storage temperature <-150C.

All FACT-NetCord accreditation takes place through the US-based Office. Currently 11 cord blood banks are FACT-NetCord accredited, with 4 of those being non-US based.

Applicable International Regulations

Dr. Warkentin described the applicable international regulations and discussed international accreditation issues such as:

- Language translation when CBB does not function in English:
- Testing for diseases uncommon in a specific country or that is not part of the routine for normal blood donors from that country.
- Labeling differences, particularly the use of the Biohazard label

Presentation by Karen Shoos-Lipton, JD

Ms. Karen Shoos-Lipton, CEO, AABB, presented an overview of AABB accreditation of sites outside of the US (see presentation 4). AABB has accredited 147 HPC and UCB facilities, with 17 outside the US

The AABB Standards Program

- Has a well defined infrastructure
- Process includes experts in the field, Ethicists, public, FDA and other orgs
- Has established timelines for updates
- Allows for interim and emergent standards
- Requires member and public comment period
- Standards developed in FDA regulated climate

The AABB Accreditation Program

- Well established program - 50 yrs.
- Designed to operate in a regulated climate
- Policies guide program
- Operates under internationally accepted standards for accrediting bodies
- Accreditation based on assessment of conformance to standards

The AABB international accreditation process is the same for all facilities with some international variances (applying to US specific details which other countries cannot meet such as testing) that are not routinely

granted.

Overall, AABB Standards comply with FDA GTPs and apply to imported products.

Karen Shoos-Lipton noted that the EU is also struggling with similar issues and that steps are being undertaken to address some of these. The Alliance for Harmonisation of Cellular Therapy Accreditation (AHCTA) is a multi-organizational group that has formed to begin work on this. The first project will be minimum import and export requirements.

Presentation by Fran Rabe

Fran Rabe, NMDP, provided an overview of the NMDP screening process for PBSC and cord blood donors of products imported into the US (see presentation 5).

US Importation of Peripheral Blood Stem Cells

In 2005, 390 units of PBSC were imported, with Germany being the primary source of these PBSCs. Fran Rabe discussed the NMDP donor screening requirements, which include a health history questionnaire, infectious disease testing and a physical exam. Details of each of these screening processes were presented. Screening is administered by the donor center/apheresis center.

US Importation of Cord Blood

In 2005, 21 units of cord blood were imported into the US. Factors that impact the screening process of cord blood donors are whether the collection of the cord blood occurred prior to or after 5/25/05 and whether the cord blood bank is an NMDP member or non-member. Different screening procedures apply based on these factors.

Presentation by John McMannis, PhD

Dr. John McMannis, MD Anderson Cancer Center presented an overview of unrelated products received from outside the NMDP structure (see presentation 6).

Dr. McMannis presented a snapshot of the current situation with unrelated transplants (developed by talking to directors from nine centers, including the top five centers based on NMDP numbers, doing a subset analysis of three of these centers, and providing a rough breakdown of numbers of products to point out trends). Ultimately, the majority come from NMDP sites, but the number coming from outside the US had been

increasing in each of the past 5 years and currently represents almost 25% of the products imported.

Furthermore the process that transplant centers use to qualify collection centers varies widely from center to center (and from product to product).

Some points to consider include:

- Do we need a better data set?
- Should there be minimum requirements for qualification of collection centers?
- Sliding scale based on clinical indication or basic minimum requirements?
- Use of FDA approved ID testing kits

Presentation by Joseph Giglio, MS, MT(ASCP) SBB, CSQE(ASQ), CQA

Mr. Joseph Giglio, AABB, presented an overview of requirement to implement the National Drug Code (NDC) system for licensed HCT/Ps including imported products as presented in the recently released rule: *Requirements for Foreign and Domestic Establishment Registration and Listing for Human Drugs, Including Drugs that are Regulated Under a Biologics License Application, and Animal Drugs* (Docket No. 2005N-0403, August 29, 2006) (see presentation 7).

Joseph Giglio noted that the NDC system is not a good fit for HPCs and TCs because:

- Biological nature/variable contents of HPCs and TCs
- HPCs and TCs are not mass-produced
- Overly burdensome with no increase to patient safety
- NDC number is not a useful reference in any federally maintained database -- products are infused/transplanted by the time the NDC number is available

Furthermore, there is a negative impact of implementing NDCs on HPCs and TCs:

- Current information systems cannot accommodate the NDC system
- Loss of standardization
- Multiple products and attributes of cellular products are not easily managed
- Overly burdensome and duplicative with no increase to patient safety

- Loss of confidentiality

Instead, there are benefits of using the ISBT 128 International Standard:

- Greater benefits and increase to patient safety than an NDC
- Globally unique product identifier
- Cellular Therapy Coding and Labeling Advisory Group (AABB, ASBMT, EBMT, FACT, ICCBBA, ISBT/ SITS, ISCT, ISCT Europe, JACIE, NMDP and WMDA)
- Industry familiarity with ISBT 128
- Excellent traceability/trackability of products
- Contains more information than the NDC code

Questions

Dr. Celia Witten asked about the current status of ISBT 128. Ms. Kathy Loper stated that documents have been finalized in their draft form, and will be posted on all the organizations websites next week (week of January 8th). The document is very international. The comment period will close on February 28th. The document will be published in May 2007 in time for the ISCT Annual Meeting, and will be published in Cytotherapy and Transfusion. Kathy Loper identified all the members of the Advisory Group and noted that at present, there is no Asian representation on the ISBT 128 Committee, but they are trying to make inroads there as well.

Dr. Phyllis Warkentin noted that not all centers have automated labeling systems. The ISBT 128 system will allow all centers to use the same terminology – but would not require that all have the same physical labeling system (some would be labeling manually, some would use automated computer systems).

FDA representatives provided clarification of the NDC issue. The proposed rule was published in August, 2006 and the comment period has been extended through the end of January, 2007. On December 11, 2006 there was a public meeting on the proposed rule. The FDA does not feel that the proposed rule is mutually exclusive of the ISBT 128.

Fran Rabe noted that we don't yet know what the licensure of these products would look like.

FDA representatives stated that the NDC preamble covers the intent – the need to know who is making the products.

Dr. Heimfeld asked the FDA if they have any comment on the import/export issues.

Representatives from the FDA asked why Germany is such a major source for the US in terms of import. Fran Rabe noted that Germany has the best established donor registry. Germany has a law where every citizen is registered with the government – the donors are easier to find, which has a huge impact on donor availability

Dr. McMannis (this might have been Fran, not John) noted that for NMDP about 11-12% of potential donors cannot be tracked down when they are matched – either they have moved or they become unwilling to donate.

Dr. Witten noted that when FDA is looking toward global harmonization, they are struggling with who their partners can or should be.

Kathy Loper suggested that the FDA should get in touch with the WMDA, adding that the German system for example, is known for requiring GMP. However, it is our understanding that there are nuances and loopholes in the system whereby the regulations do not apply to procedures involving such products if the entire collection, processing and infusion occur in a single operation or a single day.

Scott Brubaker noted that the EU Directive does not really include anything on import/export – and this will likely be the subject of a future directive.

HOMOLOGOUS USE WHITE PAPER

Presentation by Lizabeth Cardwell

Ms. Lizabeth Cardwell, Compliance Consulting, presented the work of the ISCT-developed Homologous Use Working Group (see presentation 8).

The Homologous Use Working Group and corresponding Advisory Group were formed by ISCT, in conjunction with other stakeholders, to address confusion about FDA's application of the definition for "*homologous use"* as found in 21 CFR 1271 to different types of cell-based therapies. The Working Group was assigned the task of creating a white paper to clearly identify industry concerns surrounding the regulatory definition for "*homologous use"* and to offer preliminary solutions. The Working and Advisory Groups intend this Homologous Use white paper to be a vehicle for communication to other member organizations and to the FDA CBER Office of Cell, Tissue and Gene Therapy.

Ultimately, the Homologous Use Working Group would like comment from the FDA and to publish the paper in Cytotherapy and/or other journals.

Presentation by Shelly Heimfeld, PhD

Experimental Evidence Demonstrating "Homologous Use"

For a history of the Homologous Use working group please see appendix 1.

Dr. Shelly Heimfeld presented an overview of how *"homologous use*" with cell products could be demonstrated (i.e. what animal model data or scientific evidence would need to be generated) (see presentation 9).

Discussion

1. Clarification of the Definition

21CFR1271.3

Homologous use: replacement or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic functions in the recipient as in the donor.

Proposal for consideration:

Homologous use: Intuitive or already clearly documented clinical evidence for efficacy in a specific clinical application. **It's not the product, it's the Clinical Application!**

2. Regulatory Options

Is there a way for an HCT/P to get off from the BLA track?

Proposal for consideration:

Homologous use: Intuitive or already clearly documented clinical evidence for efficacy in a specific clinical

application. **Once clinical data becomes available, product now "shifts" to meet the definition of 361**

Question for consideration: Should the Working Group be re-focused on data collection to demonstrate homologous vs. non-homologous?

A call for agenda items for the next meeting was put forth and attendees were asked to follow up with suggestions. It was decided that the next meeting would take place in June at the AABB National Office.

Appendix 1.

History of the Homologous Use Working Group

The consensus at the November 5, 2004 Cell Therapy Liaison Meeting held between the FDA and representatives of stakeholder organizations in cell therapy, was that **"a working group must be established to work on a guidance document for clarification of homologous use".**

ISCT announced establishment of the Working Group by distributing a notice inviting nominations for two positions:

(a) Expert working group – individuals who have a working knowledge of processing facilities and issues for a variety of cell types

(b) Broader advisory group – advise the expert working group by reviewing draft output and providing comment on select issues prior to seeking public comment

Nominations were to be done by the submission of a C.V. of the nominee to the ISCT Head Office no later than May 20, 2005. Self-nominations were accepted.

The Working Group's mandate was to:

(a) define and explain "*homologous use*" to the cellular therapy community

(b) simplify interpretation in a way that is equally applicable to all types of cells

(c) define scientific studies needed to assist with the definition

(d) identify potential critical path projects for FDA to assist in the definition

One of the primary goals of the Working Group was to draft a guidance document which attempts further clarification of "*homologous use*" for the cellular therapy community.