

# 1<sup>st</sup> Biannual Cell Therapy Liaison Meeting

November 5, 2004

Bethesda, MD

## Organized by International Society for Cellular Therapy Hosted by the AABB

### Organizations Represented:

American Association of Blood Banks	Foundation for the Accreditation of Cellular Therapy
American Association of Tissue Banks	International Society for Cellular Therapy
American Society for Blood and Marrow Transplantation	National Heart, Lung, & Blood Institute, NIH
American Society for Apheresis	National Marrow Donor Program
American Society of Hematology	Regulatory Affairs Professionals Society
Food & Drug Administration, Center for Biological Evaluation & Research	

### Regrets:

American Society for Gene Therapy  
International Society for Biological Therapy of Cancer

### No Response:

American Society for Testing and Materials	Cell Transplant Society
American Society of Transplant Surgeons	International Pancreas and Islet Transplant Association
Biotechnology Industry Organization	United States Pharmacopoeia

### Declined:

Biomedical Excellence for Safer Transfusion (BEST) Collaborative (formerly of ISBT)

### Attendees:

Moderator: Stephen J. Noga  
Coordinator: Lee Buckler

AABB	Allene	Carr-Greer	FDA CBER	Jesse	Goodman
AABB	Edward	Snyder	FDA CBER	Joyce	Frey-Vasconcells
AATB	Scott	Brubaker	FDA CBER	Diane	Maloney
AATB	Deborah	Deborah Butler-Newman	FDA CBER	Sherry	Lard
ASBMT	Charles	LeMaistre	FDA CBER	Jim	Cohen
ASFA	Chester	Andrzejewski, Jr.	FDA CBER	Stephen	Grant
ASFA	Lee	Clough	FDA CBER	Andrea	Wright
ASGT	David	Bodine	FDA CBER	Cynthia	Rask
ASGT	Jay	Lozier	FDA CBER	Dwaine	Rieves
ASH	Richard	Jones	FDA CBER	Mercedes	Serabian
ASH	Mila	Becker	FDA CBER	Stephanie	Simek
FACT	Phyllis	Warkentin	FDA CBER	Raj	Puri
ISCT	Shelly	Heimfeld	FDA CBER	Kim	Benton
ISCT	Dennis	Gastineau	FDA CBER	Suzanne	Epstein
NHLBI	Liana	Harvath	FDA CBER	Eda	Bloom
NMDP	Chatchada	Karanes	FDA CBER	Steve	Bauer
NMDP	John	Miller	FDA CBER	Ruth	Solomon
RAPS	Sherry	Keramidas	FDA CBER	Marty	Wells
RAPS	Linda	Temple	FDA CBER	John	Bishop
			FDA CBER	Seamus	O'Boyle

## Agenda

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

8:30-8:45 -- **Introduction** of FDA and Liaison participants

### **Definition of Homologous Use**

8:45-9:15 -- FDA (Stephen Grant, MD)

- Review of the current definition/classification for homologous vs non-homologous use

9:15-9:45 -- "Industry" (Shelly Heimfeld, PhD)

- Identification of the primary practical issues that flow from the current definition
- Examples of the practical implications of the classification between GTP (361) vs. GMP (351) in various applications or cell types

9:45-10:30 -- Input

- Discussion and clarification of the classification in various applications (stakeholder perspectives and input)

10:30-11:00 -- Consensus

- Identification of further clarification required and determination of action points

### **Combination Products**

11:00-11:15 -- FDA (Joyce Frey-Vasconcells, PhD)

11:15-11:30 -- "Industry" (Dennis Gastineau, PhD)

11:30-11:45 -- Discussion

11:45-12:00 -- Action plan

12:00-12:30 -- **Future Meetings**

- Identification of topics, protocol, and format for future meetings
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## Meeting Summary

ISCT's liaison to the FDA, Dr. Stephen Noga, commenced the meeting with opening remarks welcoming attendees to the inaugural cell therapy liaison meeting intended to take place twice per year in the tradition of other liaison meetings that take place in the blood and drug sectors. He remarked that ISCT was pleased to be taking the organizational lead in managing these meetings. He repeated ISCT's intent to ensure these meeting were truly multi-stakeholder and discussed that both ISCT and the FDA were actively soliciting both agenda items and organizations to be invited either regularly or *ad hoc*. Dr. Noga commented that the intent was that for organizations rather than individuals to be invited and that the invited organizations could then determine who should represent them at each meeting. He added that while the date and agenda for this meeting were set rather arbitrarily by ISCT and FDA, every attempt would be made to solicit more input and availability for future meetings. The meeting was then turned over to the first presenter.

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## DEFINITION OF HOMOLOGOUS USE

### Presentation #1: Dr. Stephen Grant

Stephen Grant (FDA/CBER) presented the FDA's definition and position on the distinction between homologous and non-homologous use. Dr. Grant reviewed the FDA's mission statement (Aug 2003): *"The FDA is responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable..."* and goal (66 Fed. Reg. 5447 (2001)): *"The goal of the new approach is to improve protection of the public health without imposing unnecessary restrictions on research, development, or the availability of new products. Under the new system, the regulation of different types of human cells, tissues, and cellular and tissue-based products (HCT/P) will be commensurate with the public health risks presented, enabling us to use our resources more effectively."*

Dr. Grant stated that the field of cell therapy is rapidly evolving with little precedent, limited scientific data, and much hypotheses. He stated that the regulations related to homologous use are part of an attempt to provide a tiered regulatory approach with the level of regulation proportional to the degree of risk. HCT/P's are derivatives of the human body and thus pose, at a minimum, a potential risk of transmitting infectious disease. Some HCT/P's ("361 products") may be effectively regulated solely by controlling the infectious disease risks they present.

Homologous use is one of four criteria that a product must meet to be regulated as a 361 product.

Dr. Grant introduced the basic distinction between 361 vs 351 products as follows:

- 361 products
  - Do not require pre-market approval
  - May be effectively regulated by controlling the infectious disease risks they present
- 351 products
  - Require pre-market demonstration of safety **and** efficacy

Dr. Grant stated, *"I want to make sure that everyone understands what regulations are. They do not represent individual opinions or even opinions of a particular group of people. Regulations are promulgated by agencies as directed by Congress to implement legislation. Developing regulation is lengthy, laborious process with input from experts within and without the agency, interested parties, and the general public. They are binding until rescinded or revised. Homologous use is an attempt to identify products which are intuitively effective, somewhat like it is intuitive that solid organs will be effective when transplanted. Further, since they function in the recipient as they did in the donor, the chief safety concern is transmission of infectious agents."*

Homologous use is one of the criterion to determine whether a product is a 361. There is no "in-between".

The regulatory definition of "homologous" use is *"...replacement or supplementation of a recipient's cells or tissues with a HCT/P that performs the same basic function or functions in the recipient as in the donor."* 21 CFR 1271.3(c).

*"HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent..."* 21 CFR 1271.10(a)(2)

Dr. Grant continued by stating: *“We do not look at the use of HCT/ P’s, but instead at whether it is advertised, labeled, or otherwise objectively intended by the manufacturer for a nonhomologous use. In fact, in the absence of advertising, labeling, or other indications of the manufacturer’s intent for such use, we do not require pre-market submissions. By labeling, we refer to ... any written, printed, or graphic materials that supplement, explain, or are textually related to the product, and which are disseminated by or on behalf of its manufacturer.” The “labeling” could include, for example, the title of a presentation at a scientific meeting”.*

For use of a cellular product to be considered homologous, the **intended** function of the product in the recipient should be similar, analogous, consistent with, or correspond to its function in the donor

The test for determining whether a function is similar, is as follows: *“Regulation solely under section 361 and part 1271 is not warranted unless it is **clearly demonstrated** that the use of an HCT/P in the recipient is homologous to the function the HCT/P would carry out in the donor.”* 66 Fed Reg 5447, 5458 (2001)

*“For example”, Dr. Grant explained, “promotion of HCT/ P for an unproven therapeutic use, such as curing cancer, would clearly make it inappropriate to regulate the HCT/ P solely under section 361 of the PHS Act and the regulations in section 1271. It is important that manufacturers be aware that they have the responsibility for demonstrating that their intended use for a cellular product is homologous.”*

An examples of homologous use is the administration of hematopoietic stem cells for hematopoietic reconstitution in patients:

- with aplastic anemia,
- after chemotherapy-induced bone marrow ablation, or
- with bone marrow failure due to genetic defects such as Fanconi’s anemia and severe combined immunodeficiency syndrome.

Dr. Grant discussed that the meaning of homologous use is not clear to some clinicians investigating cellular therapy. Recently, for example, some cardiologists have considered the administration of autologous bone marrow derived cells to a patient after heart attacks not to be subject to pre-market testing. *“The hypothesis behind these and other studies”, Dr. Grant explained, “is that resident cardiac cells can participate in tissue repair and are replenished by cells from the blood stream derived from the bone marrow. But clearly this hypothesis is just a hypothesis not yet widely accepted by the scientific community. The behavior of cells is dependent not only on their genotype but also on the microenvironment in which they reside and where they are placed the physical and chemical milieu into which cells are placed helps determine their phenotype.”*

Factors considered for assessing homologous use include:

- Manufacturer’s objective intent
- Similarity of function
- Sufficiency of regulation solely under section 361 of PHS to assure safety and/or efficacy

Dr. Grant made it clear that the FDA intends to revisit the concept of “homologous use” periodically, as new scientific evidence becomes available regarding the functions of various cell types. He stated, *“As I mentioned earlier, the field of cellular therapeutics is still rapidly*

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*evolving and judgments about whether particular uses are homologous have to be tentative. Indeed whether the classification will remain useful in the future is unknown.”*

Dr. Grant briefly reviewed when an IND is required for cellular therapy:

- More than minimally manipulated (needs yet to be well defined)
- Promoted or labeled for any use other than a homologous use
- Combined with or modified by the addition of any component that is a drug or a device
- Has a systemic effect and is not for autologous, family-related allogeneic, or reproductive use

Finally, Dr. Grant concluded his presentation by outlining that the following FDA requests:

- Help explaining “homologous use” to the cellular therapy community
- Help in simplifying the interpretation, but need one applicable to all cell types, not just hematopoietic stem cells
- Help in defining scientific studies needed to determine homologous use
- Potential critical path projects for FDA to undertake

One of the options Dr. Grant proposed for consideration is that industry propose a draft guidance document to FDA which attempted further clarification of homologous use.

### **Presentation #2: Dr. Shelly Heimfeld**

After providing a summary of 21 CFR 1271 and reviewing the criterion for 361 products as well as some of the critical definitions, Dr. Heimfeld provided two case studies intended to stimulate discussion.

The first case study was a multi-center Phase III registration trial in which the Fred Hutchinson Cancer Research Center is involved, entitled, “High Dose Immunosuppressive Therapy with Autologous CD34-enriched Hematopoietic Stem Cell Transplantation for Autoimmune Diseases”. He gave the following background:

- The study involves high dose chemotherapy and autologous CD34 cells (Worcester Conference, 1999)

<u>Diseases</u>	<u>Complete &amp; partial remissions</u>
Multiple sclerosis	36%
Systemic lupus erythematosus	67%
Rheumatoid arthritis	54%
Systemic sclerosis	65%
- Phase I/II studies were done under IDE at various institutions
- The phase III study is a multi-million dollar, multi-center, NIH grant-funded study

The impact of current FDA-thinking on this study is as follows:

1. The study involves autologous transplants with minimal manipulation which one would think means it would be governed under the upcoming GTP rule.
2. However, the study was designated by FDA as “non-homologous” use therefore meaning it would be governed under GMP.

The decision was made by the “Tissue Reference Group” (TRG). Questions that arose include:

- Who is the TRG?
- Why is the criteria for designation not more clearly stated?

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- Is there any forum for input, presentation, or discussion about this decision?
  - Is there any mechanism for contesting, appeal, or reclassification?
3. Classification under GMP means the study requires an IND application and ultimately a BLA. This means work such as:
- New manufacturing standards (lot release: purity, potency, etc.)
  - New facility requirements
    - HEPA filtration/Class 10,000/Class 100 BSC
    - Environmental monitoring
  - More documentation, continuous witness function
  - More quality oversight and review
  - Stability and comparability studies

Related to the requirement that a BLA would be required for all “manufacturing” sites for autoimmune transplants, Dr. Heimfeld observed that:

- (a) Academic centers have no experience in BLA process
    - Stand-alone commercial development difficult
    - No intellectual property protection
    - Not in mission statement of centers to be exclusive
    - Not volume driven business
  - (b) Cost/benefit calculations become much more difficult to justify because of:
    - Extra Facility Expenses
    - Extra Personnel Expenses – Quality/Regulatory
    - Reimbursement issues – identical procedure would now cost 3-10 times more
  - (c) The mechanism for eventual “approval” of other sites that were not part of clinical studies, is not clear.
4. The apparent inconsistency is that identically manufactured product for other patients (e.g. malignancy) fall under GTP.

The question Dr. Heimfeld posed for discussion was as follows:

Why non-homologous (351) when the study involves:

- a. autologous & minimal manipulation
  - nothing about processing will change properties of cells
- b. cells taken from blood and injected back into blood
- c. similar biological function in recipient as in donor
  - lymphohematopoietic reconstitution
- d. no intention to label/advertise for non-homologous use.

The second case study or example that Dr. Heimfeld presented was related vs. unrelated allogeneic PBSC transplants. Again, Dr. Heimfeld posed a series of questions:

1. Why are related transplants governed by 361 vs. unrelated which would have a 351 designation given that the same intense screening criteria applies to both sets of donors and:
- (a) The donor eligibility rules are similar or identical
    - GTP will “cover” communicable disease transmission
  - (b) The current clinical settings similar/identical
    - Homologous lymphohematopoietic reconstitution
  - (c) Current “Manufacturing” is similar or identical but would have to
2. The same concerns regarding BLA & facility requirements as stated above apply.

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In response to the questions posed FDA personnel provided the following responses in the course of discussion:

- There is an SOP that outlines how to meet with the TRG for determination of whether a study in question involves a “tissue”. An “appeal” of a TRG ruling is available to the FRD for re-consideration or clarification
- One plausible scenario for dealing with the onus of BLAs is where academic centers possess a BLA and share the data in the Federal Register so that other centers can use the SOPs used in preparing and administering the product. Other centers then submit “mini BLAs” based on the data in the public sector. Additionally, or alternatively a standards based approach might be possible where all the clinical data and documentation is put into a public document made available in the public domain. The NHLBI cord blood study is an example of SOPs in the public domain though in that particular study the data cannot yet be released in the public domain because the appropriate consents were not obtained (in the pre-HIPPA environment). They are interested in working with the Agency to find a way to make the data available to the FDA in a confidential and compliant manner. This may be the first example of a standards-based approach.

## COMBINATION PRODUCTS

### Presentation #3: Dr. Joyce Frey-Vasconcells

Dr. Frey began with the definition of what types of products constitute a “combination product”. A combination product is any product that is:

- (a) Comprised of two or more related components,  
(e.g., drug/device, biologic/device, drug/biologic, drug/biologic/device)  
which are physically, chemically, or otherwise combined or mixed (21 CFR 3.2(e)(1)).
- (b) Two or more separate products packaged together 21 CFR 3.2(e)(2).  
(e.g., drug/device package, device/biologic package, biologic/drug package)
- (c) Two or more separate products packaged separately where one is already approved, that based on investigational plan or labeling are intended for use only with the other approved individually specified article, and both are required to achieve intended use, indication, or effect, and cross-labeling is needed (21 CFR 3.2(e)(3))
- (d) Two or more separate products packaged separately, where both are investigational, that based on proposed labeling are to be used with the other investigational article, and both are required to achieve the intended use, indication, or effect, and cross-labeling is needed (21 CFR 3.2(e)(4))

*“The common theme in the regulatory definition of combination products”, Dr. Frey stated, “is that products are specifically intended for use together.”*

Dr. Frey then proceeded to give several examples of combination products:

Example 1:

Myeloablative therapy plus cells (e.g., any myeloablative set of drugs plus cells) is not a combination product. Why? Because, referring to 21 CFR 3.2(e)(3), this does not meet (as combination products must) all three criteria:

- Approved specified drug
- Both required to achieve effect
- Cross-labeling needed

Example 2:

Specific myeloablative drug(s) plus cells is a combination product. Why? Because, referring to 21 CFR 3.2(e)(3), this meets all three criteria:

- Approved specified drug
- Both required to achieve effect
- Cross-labeling needed

Dr. Frey then took the opportunity to mention the Primary Mode of Action Proposed Rule which was issued May 7, 2004 in the Federal Register. The purpose is to define the FDA's PMOA in such a way as to provide both internal and public clarity on how the FDA determines each center's jurisdiction. The Agency received many public comments that are currently being considered in redrafting the Final Rule.

#### **Presentation #4: Dr. Dennis Gastineau**

After giving a brief overview of the regulatory background and framework for combination products, Dr. Gastineau discussed several examples of combination products:

- Device/Drug
  - Drug-eluting stents
- Device/Biologic
  - Cell Coated Stent for biologic delivery of cytokine
- Two Products packaged as a single unit
  - Dendritic cells packaged with a cytokine/growth factor to be combined at administration
- Two products packaged separately where one is intended for use only a second approved product
  - Frozen cardiac progenitors designed/validated to be delivered through a specific approved catheter
- Two products packaged separately where both are investigational and both required for the intended effect
  - Transduced cells
  - Novel membrane capsule for implantation

Dr. Gastineau then identified a number of challenges for cellular therapy related to combination products for discussion:

- Cooperation between industry/academics
  - Example: Successful cardiac cell-based therapy based on delivery with a 510k approved catheter
    - All preliminary data based on XYZ catheter

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- XYZ corporation decides the use of their catheter in this application is not in their interest
  - What can be done?
  - Master file--company ABC has submitted a master file for a device
    - ABC company may not have any incentive for keeping the master file current
  - A master file can be closed individually (to a particular reference) or a master file can be closed broadly. What recourse does an investigator have if a master file is closed?
  - Combination products require cooperation between organizations that do not necessarily share interests. There is an increased risk of failure because of the required cooperation. For example, as companies are bought/sold, business priorities and outlooks shift and agreements are subject to change or cancellation.
  - Is there a way to mitigate the risk to business partners that is associated with their products being used in combination products so as to allow development of safe and effective new therapies?

Discussion centered around the FDA's current focus on developing specific strategies around the various types of combination products and the need for industry input as well as the submission of real-life examples of how combination products were presenting challenges.

RAPS offered to help further discussion around this issue at an upcoming combination products they are hosting.

### CONSENSUS & ACTION

ISCT, as the host organization, and the FDA need to attempt to invite others groups to participate in this forum such as tissue engineering groups and cardiac groups.

Each participating groups needs to engage in educating their respective constituents on the need for understanding and participating in the further development of the regulatory framework that is being established for cellular therapies. Potential action items to consider:

- regulatory sessions at conferences need to be given more prominence
- establishing and supporting a multi-stakeholder educational task force

A working group must be established to work on a guidance document for clarification of homologous use.

**ACTION:** ISCT will announce the establishment of this working group by distributing the notice (for circulation) to all participating and invited organizations as well as through its membership and network. The notice will include a solicitation of volunteers for an expert working group as well as a broader comment group.

**ACTION:** ISCT will solicit topics for future meetings from all participating and invited organizations as well as through its membership and network.

All participating and invited organizations should be invited to re-think the cellular therapies priority list that ISCT initially developed and submitted to the FDA one year ago.

**ACTION:** ISCT will circulate the original list for comment and discussion at the next meeting.

Each participating and invited group should be challenged to identify specific critical path project proposals that it will submit to the FDA for consideration.

Future agenda items may include the regulatory framework for autologous vs. allogeneic transplants as well as ancillary products.

The collective group should consider a workshop or workshops that can be developed or supported that will engage the broader cellular therapy community in the discussions raised in the liaison meetings. At minimum these should include the ISCT/FDA Somatic Cell Therapy Symposium, RAPS meetings, and each annual meeting of the participating and invited organizations.