

ISCT 2010 Annual Meeting, Philadelphia, PA
Global Regulatory Perspectives Workshop - May 23, 2010
Horizons Rooftop Ballroom

Chairs: **Scott Burger, MD, Advanced Cell & Gene Therapy - USA**
Karen Edward, BSc, MT (ASCP), Advanced Cell & Gene Therapy - USA

Objectives:

To provide participants with viewpoints and perspectives from international regulators of cell therapy products. Sessions will address:

- New and evolving regulations worldwide
- Status of compliance activities around the globe
- Regulatory considerations for multi-national clinical trial design and execution, and current questions and regulatory controversies.
- Case studies will cover current questions and regulatory controversies and will include panelists comprised of regulators and industry representatives.

Preliminary Program

8:00am – 8:30am	Registration
8:30am – 8:45am	Regulatory Developments - Global Overview
8:45am – 10:15am	<p>Session I – Global Regional Update Moderator: Scott Burger, MD - <i>Principal, Advanced Cell & Gene Therapy, USA</i></p> <p>Speaker: Eriko Fukuda - <i>Senior Reviewer, Pharmaceuticals and Medical Devices Agency (PMDA), Japan</i> Speaker: Chiyoung Ahn, PhD - <i>Director, Advanced Therapy Products Division, Korea Food and Drug Administration (KFDA), Korea</i> Speaker: Srinivasan Kellathur, PhD - <i>Senior Regulatory Specialist, Health Sciences Authority (HSA), Singapore</i> Speaker: Giovanni Migliaccio, PhD – <i>Director of Research, The European Agency for the Evaluation of Medicinal Products (EMEA), Italy</i></p> <hr/> <p>The regulatory environment for cell and gene therapy products is as dynamic as the products themselves, emerging and evolving regionally and topically. In some areas, regulators are planning initial regulations for these products. Agencies with established rules and standards for cell and gene therapy, however, are adapting and evolving in response to the challenges presented by particular types of products and treatment strategies, often expanding the scope of regulation, and sometimes considering multinational approaches. This session will provide an overview of these emerging regulatory environments, with examples from different regulatory agencies.</p>
10:15am – 10:30am	Coffee Break
10:30am – 12:00pm	<p>Session II – Compliance Activities Moderator: Ineke Slaper-Cortenbach, PhD - <i>Director, University Medical Center Utrecht, Netherlands</i></p> <p>Speaker: Mary Anne Malarkey - <i>Director, FDA/CBER/OCBQ, USA</i> Speaker: Jeanette Ripper - <i>GMP Auditor, Therapeutic Goods Administration (TGA), Australia</i> Speaker: Chun-Che Yen, PhD- <i>Lead auditor of GTP inspectorate, Researcher, Industrial Technology Research Institute, Taiwan</i></p> <hr/> <p>This session will give the different perspectives on how regulatory bodies or competent authorities around the world deal with compliance issues. Compliance to all aspects of cellular therapy manufacturing will be discussed, including GMP license of the facility, the details of the manufacturing procedures, QC/QA, preclinical studies and clinical studies. This session will provide insight in the strategies of regulatory bodies/CA to check for</p>

	compliance and will be especially helpful for companies intending to spread their operations to different parts of the world.	
12:00pm – 1:00pm	Lunch	
1:00pm – 3:00pm	<p>Session III – Regulatory Considerations for Multi-National Clinical Trials Moderator: Kurt Gunter, MD - <i>Global Medical Director, Hospira Inc., USA</i></p> <p>Speaker: Hartmut Krafft, PhD - <i>Co-Chair, Clinical Trials Facilitation Group (CTFG), Germany</i> Speaker: Bruce Schneider, MD - <i>Medical Officer/Team Leader, FDA/CBER, USA</i> Speaker: Jack McLane, PhD - <i>COO and VP Clinical and Regulatory, Clinquest, USA</i> Speaker: Edwin Wagena, MSc, PhD - <i>VP, Clinical Development, Kiadis Pharma, Netherlands</i></p> <hr/> <p>Although phase 1 and 2 clinical trials may be performed at one or a few sites, multi-center, global clinical trials are frequently required for product approval, and are often viewed as a gold standard for product registration. Such trials are logistically complicated because different regulatory authorities and standards of medical care may come into play, and because center-specific effects may increase overall data variance. These concerns are amplified in the case of cell therapies, as manufacturing, stability and distribution issues may further complicate the logistics. This session will explore some of the regulatory, operational and practical issues associated with conduct of large-scale clinical trials on a global scale to support approval of cell therapy products. The panel of speakers will include representatives from industry and world wide regulatory authorities to provide a variety of experience and viewpoints.</p>	
3:00pm – 3:15pm	Coffee Break	
3:15pm – 4:45pm	<p>Session IV – Case Studies Moderator: Dominic Wall, PhD – <i>Operations Director, Peter MacCallum Cancer Centre, Australia</i></p> <p>Case Study 1: Product Technical Standards Hartmut Krafft, PhD - <i>Co-Chair, Clinical Trials Facilitation Group (CTFG), Germany</i> Pam Dyson, BSc (Hons) – <i>Scientific Manager, SA Pathology, RAH, Australia</i></p> <p>Case Study 2: Facility Controlled Environments Gang Wang, PhD – <i>Biologist, FDA/CBER, USA</i> Shelly Heimfeld, PhD – <i>Director, Cellular Therapy, FHCRC, USA</i></p> <p>Case Study 3: Clinical Requirements for a Multicenter Study in Multiple Markets Hartmut Krafft, PhD - <i>Co-Chair, Clinical Trials Facilitation Group (CTFG), Germany</i> Bruce Schneider, MD - <i>Medical Officer/Team Leader, FDA/CBER, USA</i> Chaya Mazouz, BSc, Rn, MA- <i>Pluristem, Israel</i></p>	<p>The case studies are hypothetical, but are intended to spark discussion of very real questions and concerns. For each case study an industry speaker with relevant expertise will present their hypothetical answer to the issues raised by each case, and similarly an international medicinal regulator or inspector will respond. A prestigious international panel with members from leading medicinal regulatory agencies will also contribute with their views on expectations for importers and local manufacturers. Vigorous and robust discussion will be encouraged with the audience so that attendees can obtain an insight on managing these ‘worst case’ situations.</p> <p>Full descriptions below.</p>

Case Study 4: Raw Materials

Srinivasan Kellathur, PhD - Senior Regulatory Specialist, Health Sciences Authority (HSA), Singapore

1. Product Technical Standards

Paradoxically, whilst HPC-As are not uniformly regulated in Europe the European Pharmacopeia has specified highly prescriptive requirements for HPC-A manufacturing and testing, which, because of harmonisation treaties become de-facto standards in other markets that specify the EP as the defining technical standard in their markets. This case study explores this paradox.

A hematology service cryopreserves hematopoietic progenitors cells (HPC-A) and banks them for long term storage in vapor storage LN₂ tanks at with an alarm limit set at -130°C. After 10 years of successful operation a new European monograph (EP monograph 2323) comes into effect for Hematopoietic Stem Cells which becomes the *de facto* product standard for the local medicinal agency. A product evaluator from this agency determines that the product storage does not comply, which mandates that these products must be stored at -140°C or lower. As the alarm sensor is set in the upper part of the tanks, setting the alarm so that corrective action can be taken before the temperature exceeds -140°C results in an alarm each time the lid is opened.

- If the facility wishes to persist with -130°C what further action or evidence might the regulator require? What defense is open to the facility?
- How should these technical standards be interpreted?
- What recourse is there if a non-binding standard in one market is used as mandatory standard in another?

The same agency cites EP monographs 2.7.23 (Numeration of CD34/CD45+ cells in haematopoietic products) and 2.7.24 (Flow cytometry) to request information on whether the test uses validated methods for sensitivity, accuracy, reproducibility and speed. Citing EP 2323 the agency then asks what the target specifications are for different stages of production (i.e. post-apheresis) and finally asks for data on quantitation of nonviable CD34's even though the gating strategy proposed by the manufacturer only reports viable CD34's.

- What approach can the facility use to validate these methods?
- What recourse is there to a facility that prefers not to use a target specification for CD34+ cells in incoming product because collections are aggregated to make a clinical dose?
- How should a facility incorporate EP requirements that propose a different gating strategy to received approaches such as the ISHAGE consensus guidelines?

2. Facility Controlled Environments

There have been substantial changes in the requirements for controlled environments with international harmonisation defined in ISO air classes as well as the PIC/S annexes spelling out new facility requirements. Facilities built using the old paradigm of a Class 10,000 cleanroom with uncontrolled areas outside will find themselves out of step with newer guidelines specifying further controls on the external environment. This case study explores this issue.

A facility has been established and running using a local standard equivalent to Class 100 /Class 10,000 cleanroom standards to make a regenerative medicine product. This cleanroom has an unclassified exterior laboratory where operators are able to wear gowns over outside clothing, but operators wishing to work in the Class 10,000 cleanroom remove their outside garments in the facility entrance, change into scrubs, and then overgown with sterile garments in the 10,000 gowning room. In the meantime the PIC/S Guide to Good Manufacturing Practice for Medicinal Products - Annex 1 Manufacture of Sterile Medicinal Products (PE 009-8 (Annexes) 15 January 2009) is mandated as the relevant standard by the local regulatory authority. This facility translates this as a Grade A (in operation) [ISO5] /Grade B [ISO 7] cleanroom without a Grade C [ISO 8] or D exterior environment. An auditor inspecting this facility determines that the PIC/S standard requires this facility to have a Grade C area with a Grade D gowning zone where all operators are required to remove outside clothing and gown, with further degowning and regowning as they move into the B grade area. The facility believes that it would need to reconfigure their gowning areas, provide filtered air to the unclassified area to meet Grade C requirements and furthermore they feel this would be

burdensome to operators particularly if they are only working in this new Grade C zone. Furthermore the facility explains that no actual manufacturing takes place in the Grade C area with all open steps only taking place in the Grade A zone supported by the Grade B environment.

- Can a facility differentiate in the gowning requirements between those traversing a Grade C zone to enter a B zone as opposed to those only working in the C grade area?
- What further corrective actions are available to the facility?
- If the facility uses EP 2.6.27 (microbiological control of cellular products) rather than EP 2.6.1 (sterility) [thus avoiding a label claim of sterility] does this have any impact on the requirements for the facility?

This same facility has a pass-through box connecting the unclassified laboratory to the Grade B cleanroom for starting materials and other reagents. The pass box has interlocked doors but does not have its own filtered air supply, depending upon the much higher pressure in the Grade B cleanroom to ensure that only clean filtered air enters the pass box. A manufacturing auditor is concerned that non-sterile biopsy containers are brought into the facility through the pass box with only surface wiping of the biopsy container with a cleaning agent and that this might compromise the facility.

- What evidence might the auditor require to show this is an acceptable practice?
- What further actions might be advisable?
- Is a pass box with its own air supply an essential requirement?

3. Clinical Requirements for a Multicenter Study in Multiple Markets

The requirements for manufacturing and trial approvals when conducting a clinical trial using a CMO in another market to service multiple markets are complex, even more so when various different product technical standards and multiple agencies are involved. This case study explores this situation from various aspects with a particular focus on clinical and testing issues.

A small cell therapy company is conducting a multi-national, pivotal clinical trial of T_{reg} cells in treatment of graft versus host disease (GVHD) following unrelated allogeneic hematopoietic stem cell transplantation. The company is located in the United States and has a contract manufacturing facility in Germany. The clinical trial sites are located in Germany, France, UK, Canada and the US. The company is ultimately seeking regulatory approval in the US (BLA) and Europe (EMA centralized application).

The manufacturing process involves collection of peripheral blood mononuclear cells (PBMC) from an unrelated cell donor (located anywhere in the world), shipment of the PBMC collection to the manufacturing facility in Germany, a three week manufacturing process, and shipment of the final product to the clinical sites. The product is intended for treatment of severe GVHD and it is therefore important to manufacture and ship the product without delay. The product has an expiration dating period of 72 hours and is shipped in the fresh state.

1. Considering the company headquarters (US), manufacturing facility (Germany), clinical trial sites (Canada, France, Germany, UK and US) and the donor country of origin (from worldwide donor registries)
 - What regulatory approvals are required to conduct this study?
 - Are there also requirements for manufacturing approval?
 - What impact does the location of the intending ultimate market approval have upon the trial approval?
2. The product is shipped in the fresh state before final sterility testing is complete. The company conducts sterility testing per USP as well as EP 2.6.27 requirements. During the study, one product, released to a site in Canada, fails the USP sterility test, but not the EP (microbiological control of cellular products) test from samples taken at release. The product has already been administered to the patient on the basis of release testing as per USP and EP samples taken earlier during culture as this is a fresh product release.
 - What action should the company take?
 - What reporting and action would the trial regulators require?
 - If the product was released to a UK site, would that change the outcome?
 - If a repeat test sample was negative by USP would that change anything?

3. An unexpected serious adverse event occurs during the clinical study in the US which meets reporting requirements. However the event does not meet reporting requirements in the UK.
 - To which clinical sites and which regulatory authorities should the sponsor report the adverse event?
4. Follow up testing of a donor 3 months after PBMC collection reveals that he/she has recently converted to HBsAg positive status. The affected product was shipped to France.
 - What are the follow-up and reporting requirements?
5. As a result of the above, the local ethics committee in France requests additional donor testing and re-testing of the product for transmissible agents upon importation into France.
 - How does this affect the conduct of the study and additional product testing vis-à-vis other countries?

4. Raw Materials

Raw materials for manufacturing and their continued availability is one of the recurrent challenges for any cell therapy manufacturer. This case study explores one of the common features of such a situation.

A manufacturing facility which makes human tissue-based therapeutics uses an enzyme available from a single manufacturer to free confluent cells from culture vessel prior to passaging. It has a specification which allows release of this enzyme from facility quarantine based upon a detailed Certificate of Analysis from the supplier reporting the ability to liberate another similar cell type within a time interval. This enzyme has appropriate safety testing based upon pharmacopoeia methods. The auditor from the local (non-US) regulatory authority cites USP 1046 (Cell and Gene Therapy Products) that this enzyme must be subjected to a specific QC characterization test performed by the manufacturer to show that each lot of material meets the requirements for intended use on this specific cell type.

- What types of test would this agency require?
- What are the options for the manufacturer to demonstrate this requirement efficiently?
- Can an auditor cite an informational chapter from USP as a requirement for a manufacturer?

The manufacturer and supplier of this enzyme is sold to a new entity which decides to revise the Certificate of Analysis to harmonise it with their own product range. They delete a statement “for further manufacturing” and replace it with “for research purposes only”.

- What impact does this have upon the manufacturer?
- If the new manufacturer changes the endotoxin testing to a non-compendial method what will be the impact?

When the service carefully reviews all of its materials it discovers that the culture media used also supplied by the new manufacturer for long term culture of the tissue now contains significant amounts of recombinant insulin. However the cells are formulated in another solution, a balanced salts preparation, free of insulin prior to administration. The supplier also states that this is “for research use only”.

- Other than qualifying an alternate product, what defense is open to the facility?

4:45pm – 5:00pm

Closing Remarks