FOUNDATION FOR THE ACCREDITATION OF CELLULAR THERAPY

FREQUENTLY ASKED QUESTIONS: STANDARDS FOR IMMUNE EFFECTOR CELLS

1. **Where can we find these Standards?**
   For clinical programs that also perform hematopoietic cell transplantation (HCT), the requirements are incorporated into the current edition of the *FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration*. All requirements in these Standards apply to immune effector cells (IECs) as they are relevant (i.e., IECs must be fully incorporated into the program's Quality Management program, personnel training programs, and process controls).

   For clinical programs that do not perform HCT transplantation, a stand-alone document is available, entitled *FACT Standards for Immune Effector Cells*.

   The Standards are available for free download on the FACT website at FACT Store. Printed copies are also available for purchase on the FACT website.

2. **What types of products fall under the FACT IEC Standards?**
   Immune effector cells (IECs) are defined by FACT as cells, in vitro modified or not, that have differentiated into a form capable of modulating or effecting a specific immune response. This includes T cells, tumor infiltrating lymphocytes (TILs), natural killer cells, dendritic cells, and mesenchymal stromal cells. Final products include, but are not limited to, genetically modified chimeric antigen receptor T cells (CAR-T cells), CAR-NK cells, genetically-modified cord blood, gene-edited products, and dendritic cell vaccines. Hematopoietic progenitor cells that differentiate into immune effector cells are also within the scope of the Standards. This broad designation includes cellular therapy products with widely diverse manufacturing methods, constructs, clinical indications, and safety and toxicity profiles.

   There are some products that do not fall under the IEC Standards because they do not meet the FACT definition of IECs. Examples include cells used for transplant grafts (they do not modulate or effect a specific immune response) and bispecific T cell engagers (BiTEs; they are not cells).

3. **Which Standards cover donor lymphocytes for infusion (DLI)?**
   Donor lymphocyte infusion is a cellular therapy most commonly used following an allogeneic transplant to treat residual or recurrent disease. The product is a leukocyte concentrate, most commonly derived from an apheresis collection [MNC, Apheresis] and administered in various doses as measured by T-Cell dose. This therapy and the products used are within the scope of allogeneic transplantation program accreditation. If similar products are used in a stand-alone immune effector cell program as an immunologic method to treat disease, this would be within the scope of IEC accreditation also.

Both the *FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration* and the *FACT Standards for Immune Effector Cells* include the definition of donor lymphocyte infusion. The therapy and the products are within the scope of allogeneic transplant accreditation and would be included in immune effector cell accreditation if utilized.

4. **We do not currently administer IECs on our HCT unit, nor do our transplant attending physicians oversee any IEC administration. How is our program expected to comply with IEC-specific standards?**
   If you are not utilizing any IEC products, these standards do not apply to the HCT clinical program and you should check IEC-specific standards in your compliance application as "NA" (not applicable). However, these products are becoming more common. If your program begins using IECs, you must be in compliance with these standards as part of starting the new activity. If a standard does not specifically state IECs as the scope of the requirement, take care to determine if the standard applies to your program. For example, cytokine release syndrome frequently occurs after administration of chimeric antigen receptor (CAR) T-cells; however, it has also been reported following haploidentical HCT. Therefore, standards referencing SOPs and training for cytokine release syndrome may apply to the allogeneic transplant program in the absence of IEC therapies.

5. **How do we know if our FACT-accredited clinical program must comply with the IEC requirements if we work in conjunction with a non-accredited service?**
   Generally, any care provided to patients as part of the FACT-accredited clinical program must comply with these standards. This includes administration of these products on your inpatient unit, in your outpatient facility, or under the supervision of your attending physicians. Several different models of care have been adopted by institutions with a FACT-accredited HCT or IEC program. Sometimes IEC products are administered by different departments, such as lymphoma, leukemia, or solid tumor departments, that are not part of the accredited program.

   For example, FACT does not require TIL administration to fall under the scope of a HCT program (and therefore to follow FACT Standards) if the attending physician is not a part of the HCT program and the product is not administered on the program's inpatient unit or in its outpatient facility.

   FACT does not dictate how an IEC program must be organized or managed, and it is not possible to list every scenario and how the standards apply. For specific questions about your program's responsibility to meet the standards, contact FACT at 1-402-920-7001 or fact@factglobal.org.

6. **What are the eligibility requirements for Clinical Programs to become FACT-accredited for IEC therapy?**
   FACT-accredited HCT clinical programs providing IEC therapy must do so in compliance with FACT Standards and apply for this accreditation at the time of the next renewal, at the latest. There is no minimum number of IEC recipients who must have been treated prior to initial IEC

accreditation in association with transplant accreditation. Compliance must be established as part of starting this activity, the activity must be reported to FACT, and documentation of compliance will be confirmed via the next renewal application process. If a program wishes to specifically achieve FACT accreditation for IEC therapy and be listed as such on the FACT website before the next renewal cycle, it may request a mid-cycle add-on inspection.

Clinical programs that are separate from HCT programs and are applying under the FACT IEC Standards must have administered IECs to at least five new patients within 12 months prior to initial IEC accreditation.

7. **Our institution's separate leukemia, lymphoma, or hematology/oncology services administer IECs and want to become FACT-accredited. May we share our accreditation?**
FACT will apply its long-standing eligibility requirements for clinical programs to IEC programs. To share an accreditation, clinical services must have shared leadership, quality management programs, and staff training protocols; and demonstrate regular interaction. Contact the FACT office for more guidance if needed.

8. **Does our clinical program need to be reinspected to be accredited for IECs?**
IEC processes at FACT-accredited HCT clinical programs are expected to be in compliance with FACT Standards upon starting this activity. Reporting of this activity and documentation of compliance will occur at the next annual report and regularly scheduled, or add-on, on-site inspection. After compliance with all Standards has been documented, the program will be accredited for IEC therapy in addition to HCT and listed as such on the FACT website. An on-site inspection, either as part of renewal accreditation or as an add-on, is required for the program to be listed on the FACT website as IEC-accredited.

   For clinical units that are not FACT-accredited, such as oncology or leukemia programs that are separate from the HCT program or non-FACT accredited transplant units, a complete on-site inspection will be required to achieve accreditation. There is no reciprocity for clinical unit accreditation by an accrediting body other than FACT. This on-site inspection will include collection facility and the processing laboratory unless previously FACT-accredited collection and processing facilities are utilized.

9. **What training requirements for GxP are expected for Clinical Programs?**
Clinical staff are responsible to understand and implement the GTP regulations in CFR 1271 as they pertain to donor screening and eligibility determination (including all four elements of eligibility: review of medical records, physical exam, medical history, and donor testing), use of ineligible donors, when to test donors and when it is not required by law but may be good medical practice or part of institutional protocols, what tests to use, reporting responsibilities, positive microbial test results, etc. 1271 GTP regulations should be part of GxP training for all areas of the program, including clinical. Good documentation practices also apply.

10. **Do these Standards apply to the collection of cells, such as mononuclear cells by apheresis, whole blood collection, or via other tissue sources?**
    The clinical standards apply regardless where the cell collection occurs.

    The IEC Standards do include requirements for cellular therapy product collection. All of these requirements are also included in the HCT Standards.

    FACT-accredited clinical programs must use collection facilities that comply with FACT Standards for collection of cells for further manufacture into immune effector cells under investigational new drug (IND) applications held by the program or its physicians as principal investigators. Verify your collection processes for IECs are in compliance with the FACT-JACIE Standards or IEC Standards as applicable to the scope of the facility's collection activities. If you are utilizing a collection service that is not currently FACT-accredited, that service must be inspected for compliance with FACT Standards.

    Clinical programs that utilize IECs manufactured by a commercial entity under either industry-sponsored INDs or FDA-approved Biological License Applications (BLAs) (or equivalent) are not required to qualify the collection facility.

11. **If our clinical program does not administer IECs, what is the responsibility of our collection facility if it collects cells for further manufacture into IECs for a third party?**
    FACT-accredited collection facilities that collect cells for further manufacture into IECs, regardless for whom the cells are collected, must do so in compliance with FACT Standards. Such collections must be fully incorporated into the facility's quality management program, personnel training programs, and process controls.

12. **We collect cells for further manufacturing by a third-party company. These donors do not always have infectious disease testing results within the prescribed period. How can we manage this?**
    Manufacturing of these products, including the donor testing for communicable diseases, is governed by a Food and Drug Administration (FDA)-approved investigational new drug (IND) or equivalent. If the IND requirements differ from the SOPs of your collection facility, it is expected that the IND will be followed and that the Collection Facility Quality Management Plan defines the processes to follow when collections are non-compliant with the usual standards or facility SOPs.

13. **We manufacture our own IECs in our FACT-accredited cell processing facility under IND. Do these Standards apply?**
    The clinical standards apply regardless where the cell manufacturing occurs.

    Accredited cell processing facilities involved in the manufacture of products under IND must also seek FACT accreditation for the "more than minimal manipulation" activities, which would include immune effector cell products. The Standards that apply to these activities are included in Section D Processing Facility Standards of the FACT-JACIE HCT Standards, the

FACT IEC Standards, and the *FACT Common Standards for Cellular Therapies*. Which Standards apply to the facility depends on the scope of activities.

Preparation for administration is not considered part of manufacturing. Therefore, processing facilities that receive, store, and distribute IECs for administration must perform these activities in compliance with the Standards but are not required to be accredited for more than minimal manipulation solely for this activity.

14. **We obtain IECs for administration in our accredited HCT program from a Good Manufacturing Practice (GMP) laboratory on our campus that is not related to our usual FACT-accredited cell processing facility. What standards apply to this situation?**
The clinical standards apply regardless where the cell manufacturing occurs.

    The GMP laboratory may already be FACT-accredited under the Common Standards. This accreditation is sufficient.

    FACT-accredited clinical programs must use processing facilities that comply with FACT Standards for cell processing under investigator-sponsored IND applications. Verify your processing of IECs is compliant with the FACT-JACIE Standards or IEC Standards as applicable to the scope of the facility's processing activities. If you are utilizing a processing service that is not currently FACT-accredited, that service must apply for and be inspected for compliance with FACT Standards within the next accreditation cycle.

    Clinical Programs that use IECs manufactured by a commercial entity under either industry-sponsored INDs or FDA-approved BLAs (or equivalent) are not required to qualify the processing facility. Written agreements with providers would be expected.

15. **If our clinical program does not administer an IEC product (e.g., a commercially licensed TIL product), what is the responsibility of our accredited processing facility or clinical program if we receive the final product prior to administration by a different department?**
FACT IEC Standards apply to any portion of the process of delivering IEC therapy that is performed within a FACT-accredited program. If the program is responsible for any steps related to the final product, including but not limited to receipt, storage, preparation for administration, or distribution for administration, these activities must be in compliance with the Standards. For example, an accredited facility that is responsible for short-term storage of a final TIL product must provide the storage in a clean, secure facility with appropriate environmental monitoring and chain of custody among other requirements in the standards.

16. Are IEC final products required to be labeled with ISBT 128 labels even if the pharmaceutical company provides its own label?

FACT does not require the relabeling of licensed products that are already labeled with a regulatory-approved finished product label prior to administration. FACT requires ISBT 128 labeling during collection of starting materials and during processing that is performed in-house for clinical trials. In the event that ISBT 128 labels for collection of cells for further manufacture (also referred to as ISBT 128 split labels) are being used by institutions and pharmaceutical companies during the course of the collection, processing, and administration of IEC products, the FACT-accredited program must follow the FACT Standards related to ISBT 128.

17. Who will perform the on-site inspections for IEC Programs?

As with all FACT on-site inspections, the volunteer inspectors will be experts in the field, active in the area they inspect, and specifically trained in FACT Standards and accreditation requirements. All clinical inspectors are physicians. Training modules related to immune effector cells are included within the training requirements for FACT clinical inspectors. Those physicians involved with immune effector cells who are not part of a transplant program or who have never been FACT clinical inspectors will be trained in the aspects of FACT Standards and Accreditation needed to fulfill this responsibility, and in the modules specific to immune effector cells.

Additional training is available for inspectors, including unique issues related to collection of cells for further manufacturing, chain of custody and identity, transportation, and shipping.

FACT processing inspectors who are trained and experienced in the inspection of laboratories for "more than minimal manipulation" activities, including manufacturing of immune effector cells and other products under IND, conduct inspections of processing facilities that manufacture IECs.

18. How do we apply to become FACT-accredited?

You should apply to become FACT-accredited when you are confident that you meet each of the requirements in the applicable Standards. The first steps are to obtain the Standards available on the FACT website (see question 1) and verify your eligibility (see question 5). If you are eligible, applications for accreditation are submitted via the FACT Accreditation Portal, found on the website. Contact the FACT office with any questions.