Selecting the Right Biomaterial Product

Regulatory Considerations and Terminology in Leukopak Collections

Key highlights:

- Understanding the goal of your clinical research helps to focus and/or reduce the specific requirements considered when sourcing starting materials.
- Definitions of material terms: RUO, GTP vs. GMP.

Executive Summary:

Navigating the regulatory and compliance guidelines for source materials like leukopaks or other human blood products for the emerging cell therapy market involves having a clear understanding of your research goals. Any study involving human subject research for a test article, like an investigational therapeutic, biologic or device, is classified as a clinical investigation, or clinical trial, and is held to strict, specific FDA guidelines. It is incumbent upon the researcher or their affiliate procurement department/ organization to ensure the research goals align with the product type procured. Though any number of organizations provide starting materials for clinical research, many use varying terms or product tiers to promote differences in their suite of leukopaks and other products, making navigating the market difficult without uniform terminology and consistency.

Definitions of Product Types

Several different types, or tiers, of leukopak products are available on the market. Many companies refer to different tiers of products by different branded or descriptive names, further complicating the matter.

Research Use Only (RUO) Products

Research use only (RUO) products are materials used for projects in the investigation phase. Under the regulations, RUO products **are not required** to undergo infectious disease testing, and the company selling the product **is not required** to register with the FDA.

Two federal regulations under 45 CFR 46 - Protection of Human Subjects are in place for RUO cellular and tissue products:

1) The product must be labeled **"For Research Use Only. Not for use in diagnostic procedures."**
2) Human tissue must be procured under an IRB protocol, or sourced from someone who has obtained board-informed consent from the subject.

Because these products are intended for early investigation and have fewer guidelines surrounding their production and procurement, they are often the most cost-effective leukopak products for research and development. While this makes them appealing, it is important to be aware of key considerations and

risks. First, not all sites selling RUO-grade tissue products are registered with the FDA or any federal agency. **To mitigate this, it is incumbent upon the researcher to determine whether their source is FDA-registered.** The FDA maintains a directory of all sites that have been registered for more than a year.* If research is part of a federal grant, material providers must provide a Federalwide Assurance (FWA) number. If materials are not consented appropriately, the data in your scientific papers can be affected, and published scientific papers could be retracted. Additionally, the research could lose critical data that would help researchers publish and require the study to be redone.

Further, not all sites that sell RUO-grade tissue products have oversight by an institutional review board (IRB). Informed consent and consent for procedure are frequently misunderstood in the medical community. Most researchers know to get an IRB for their research but fail to ask if the materials sourced are likewise approved by an IRB. It is important to note is that some NIH grants require an IRB Certificate of Conformance to verify that the IRB follows all federal guidelines. **To mitigate the risk of procuring a product that is not collected under IRB oversight, ask the company for a copy of the Certificate of Conformance or an IRB protocol.** Lastly, because infectious disease testing is not required for RUO products, the type and quality of IDT testing performed across RUO leukopak providers varies. **Be sure to ask for clarification from your material provider to ensure your RUO leukopaks receive the level and quality of infectious disease testing needed to prevent contamination in your research and to protect your staff as necessary.**

Current Good Manufacturing Practice (cGMP) Products

cGMP leukopaks are often referred to as "commercial grade," "gold standard," or "GMP suitable." There are several regulatory nuances to be aware of when procuring a product identified as cGMP leukopak. cGMP products are not collected under federal guidelines 21 CFR 210/211. Some cGMP products can be collected under 21 CFR 606 titled "Current Good Manufacturing Practice for Blood and Blood Components." These regulations cover both allogeneic and autologous transfusion. In addition, infectious disease testing must occur and be disclosed in the case of further manufacturing.

Current Good Tissue Practices (cGTP) Products

Implemented in 2001, FDA 21 CFR 1271 creates an electronic registration for organizations that manufacture human cellular and tissue-based products. Products collected under these guidelines are classified as cGTP products and have specific requirements around donor eligibility, operational standards and procedures preventing the introduction, transmission and spread of communicable diseases. Further specific regulations in 21 CFR 1271 for manufacturers of devices and drugs tie into 21 CFR 210/211 and include practices on environmental monitoring, tissue/cellular product manipulation beyond collection, and stringent IDT requirements 30 days prior to, as well as during, the collections procedure. Lastly, pooling of cGTP products is not permitted.

Differences between cGMP and cGTP Products

cGTP or cGTP-grade products are required for any trials later than phase 1, or for research specific to new devices, drugs or biological submissions. In both product categories, a Certificate of Analysis (COA) that details infectious disease testing results, as well as the inclusion of any user-defined criteria, will be provided.

Key Differences Between Commercial-grade Product Tiers

cGTP

cGTP products cannot be pooled and must come from a single donor/contributor. Products are collected under federal guidelines 21 CFR 210/211. (21 CFR 1271)

cGMP

cGMP covers any general biologic product (CFR 600-680), whereas processes containing any human cell or tissue, cGMP regulations would apply. cGMP products are not collected under federal guidelines 21 CFR 210/211. (21 CFR 1271)

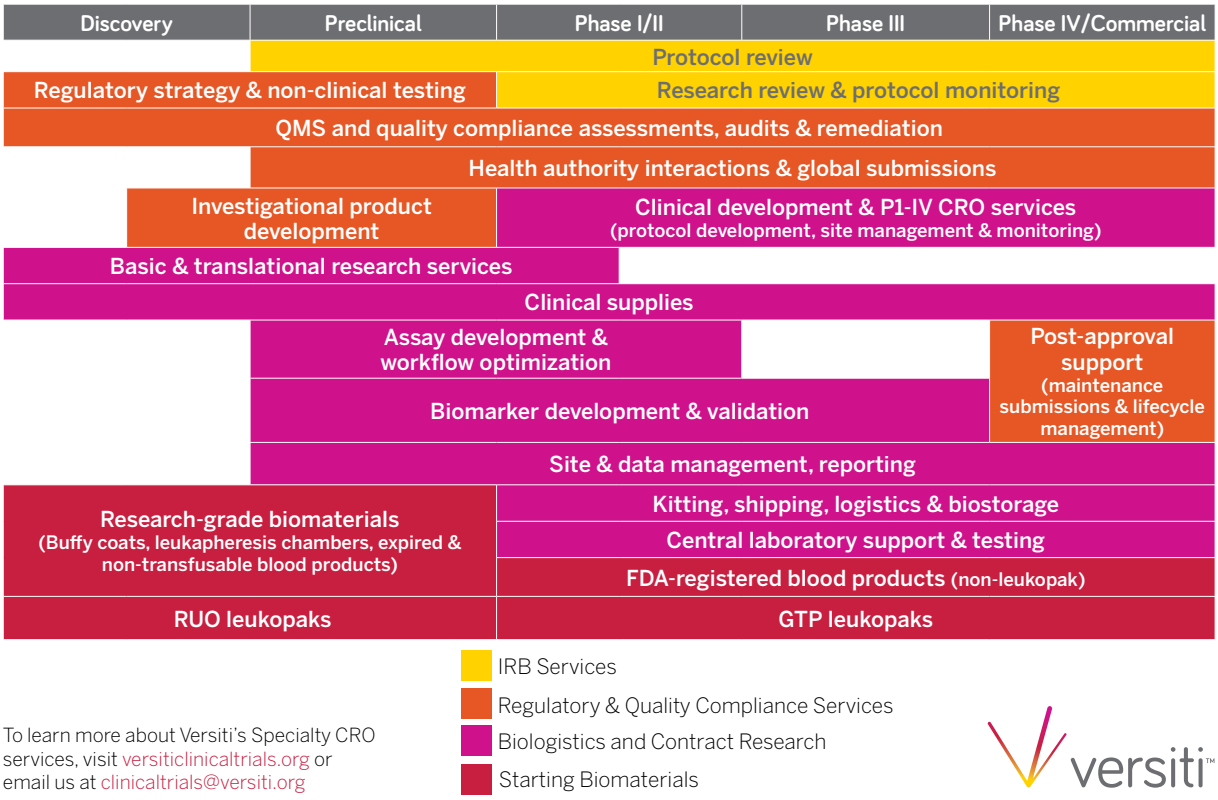
Versiti Specialty CRO Capabilities

Guiding Appropriate Product Selection

For 75 years, Versiti's vertically integrated product testing and characterization and robust quality and regulatory expertise have assisted clients in selecting the optimal products for their projects. Our experience navigating the regulatory environment fosters a unique partnership with clients, building research protocols that support the types of products needed throughout the research and clinical trial pipeline.

Versiti Clinical Trials - Contract Research Capabilities

Versiti provides expert support for a diverse range of clinical trial needs. Our comprehensive approach includes logistics, IRB services, central laboratory services, blood products for research, and more. We are your partner throughout every stage of your clinical or academic research.



To learn more about Versiti's Specialty CRO services, visit versiticlinicaltrials.org or email us at clinicaltrials@versiti.org

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Case Highlight

Client Need: Currently in phase 1 clinical trials, the client sought to identify and maintain a unique, eligible contributor pool to support their project. Both RUO and cGTP leukopaks were needed to support further research and future manufacturing.

Consultative Approach

Versiti's dedicated project management team conducted multidisciplinary meetings with the client to understand the specific contributor characterization need and worked to develop a custom recruitment and identification process.

Contributor Screening

Versiti quickly queried our existing, highly characterized contributor base for matches. We saved the client time through our robust baseline characterization (HLA and ABO typing, plus standard infectious disease testing) and in-house lab and logistics solutions, which allowed for additional characterization to meet project specifications.

Contributor Selection

Versiti's expertise in contributor management included expanded contributor interviews and screening used to protect a dedicated contributor pool for future collections. This led to four dedicated contributors for the client. These contributors matched the client genotype and phenotype donor characterization profiles and were thoroughly tested in to produce quality products in a trial manufacturing run.

Collection and Shipment

Versiti's comprehensive approach provided expanded infectious disease testing panels, as well as custom labeling, certificates of analysis and logistics to meet our client's needs, and expedient delivery customized to the client's specific manufacturing schedule.

Solution

Through a collaborative partnership and dedicated contributor pool, Versiti's vertically integrated services met the needs of our client, aligning GTP collections to their manufacturing schedule.

Summary

There are many leukopak and human blood product starting material providers on the U.S. market today, ranging from large commercial collection firms to distributors and independent blood banks. All these organizations work within the same regulatory framework; however, no universal commercial terminology related to the tiers of products for clinical research have been accepted across the industry, creating a lack of clarity when sourcing products from providers.

Further complicating the process, ensuring compliance within the regulatory frameworks is the responsibility of the study site and principal investigators. It is essential to understand which questions to ask of your material providers to ensure a successful journey throughout each phase of the clinical trial pipeline. Having a partner like Versiti, with expertise not only in collections, donor management, infectious disease testing and product characterization, but also robust and dedicated quality and regulatory expertise, helps to ensure your projects progress smoothly throughout the duration of your research.

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