Cell Therapy Development and Manufacturing:

Regulatory & Supply Chain Considerations for Human AB Serum

Cell Culture – Overview

Cell culture enables the controlled growth of cells outside their natural environment. It is central to the manufacture of biologics, monoclonal antibodies, and increasingly, cell therapies. Cell culture success relies on raw materials such as media, reagents, and serum to replicate in vivo conditions and promote optimal cell growth. Cell culture in biotechnology involves the in vitro culturing of cells for an expected benefit. In the case of biotechnology applications, cells have been modified to express proteins and other substances that can enhance human conditions like human growth hormone and erythropoietin. Cell culture can also provide a platform for drug discovery and toxicity testing of novel compounds in the search for new therapeutic drugs.

Recently, cell culture has played a major role in the advancement of cell therapies and in particular, chimeric antigen receptor T cells (CAR-T) by allowing cells that have been removed from a patient to be modified and expanded outside the body so that the cells can be delivered back to the patient to fight different types of cancers. One major reason for the success of cell culture is the use of serum as an additive to promote cell growth.

Serum, particularly human male AB serum, is vital in cell therapy manufacturing for its role in enhancing cell proliferation by providing nutrients, growth factors and cytokines, reducing mechanical shear, and binding toxins[1,2]. Other serums like fetal bovine serum (FBS) and calf serum have been used as a main ancillary material in the production of bio-molecules. Unlike FBS and calf serum, human serum eliminates xenogenic risks and is therefore preferred when production of cells for therapeutic use is being performed.

Cell Culture for Cell Therapy – The Use of Human Serum

What is Human Serum

Serum is the non-cellular portion of blood, post-clotting, containing proteins, cytokines, growth factors, hormones, and nutrients. In the context of manufacturing human serum, blood is collected from donors either with or without anticoagulants depending on the method used for collection. For serum, the cells and clotting factors are removed by allowing the whole blood or plasma to form a clot. This clot is removed and what is left is the liquid portion of blood or serum. Serum donations from multiple donors can be pooled and filtered to create a serum product which can be used as an additive in cell culture.

Rationale for Human Serum in Cell Culture

Different types of serums have been used in cell culture like FBS and calf serum and these have proven to be workhorses in mammalian cell culture in research and for the production of bio-molecules by showing improved cell proliferation, viability and reduced toxicity[2,3]. The nature of these animal-derived serum products poses a risk of potential xenogenic transfections and other reactions which does not make FBS or other bovine derived products a viable long-term serum alternative for cell therapy production. Human serum plays a critical role in cell therapies as a growth promoter and protector of cells. Human serum removes the potential xenogenic risk and gives human cells a culture environment that mimics the native environment. Human serum should be the preferred growth supplement for cell therapy applications due to its inherent biocompatibility in human therapeutic manufacturing.

Additionally, while it may provide some familiarity for research purposes, it is important to use the correct serum-type at the start of your project to avoid any unforeseen challenges in transitioning to a different serum type later down the road. This prevents unnecessary rework, testing, or even costly bridging studies during clinical development.

Rationale for Male AB Serotype Human Serum

Human serum from males with blood type AB is the preferred serum used in cell therapy applications because the blood cells of these donors have antigens for both A and B blood types and as a result, there are no antibodies for either blood type A or B in the serum. Due to the absence of these A and B antibodies in serum, human AB serum (HABS) has a lower immunogenicity risk for cell therapy products. Male donors are also preferred due to the absence of major histocompatibility complex (MHC) antibodies, making it more suitable for cell therapy applications[4].

Sources of Human Serum

There are typically three different types of human serum that are available for use in cell culture applications: Normal Human Serum (NHS), Plasma Derived Serum (PDS), and Off-the-Clot (OTC).

Normal Human Serum

Normal human serum consists of a pool of donors from any and all blood types from male and female donors, meaning antibodies to the A and B blood types are present. Due to the variability that can occur based on the complexity of the final pool, this material is not typically used in cell culture applications.

Plasma Derived Serum from Male AB Donors (PDS)

Plasma derived serum is manufactured from plasma donations acquired through plasmapheresis and treated with thrombin to remove fibrin and clotting factors. The conversion process from plasma to serum can use either bovine thrombin or human thrombin. Plasma derived serum allows for risk mitigation due to the volume of plasma commercially available. Plasma donations can be made once in a two-day period and twice within a seven-day period[5], supporting donor frequency and limited donor pool sizes.

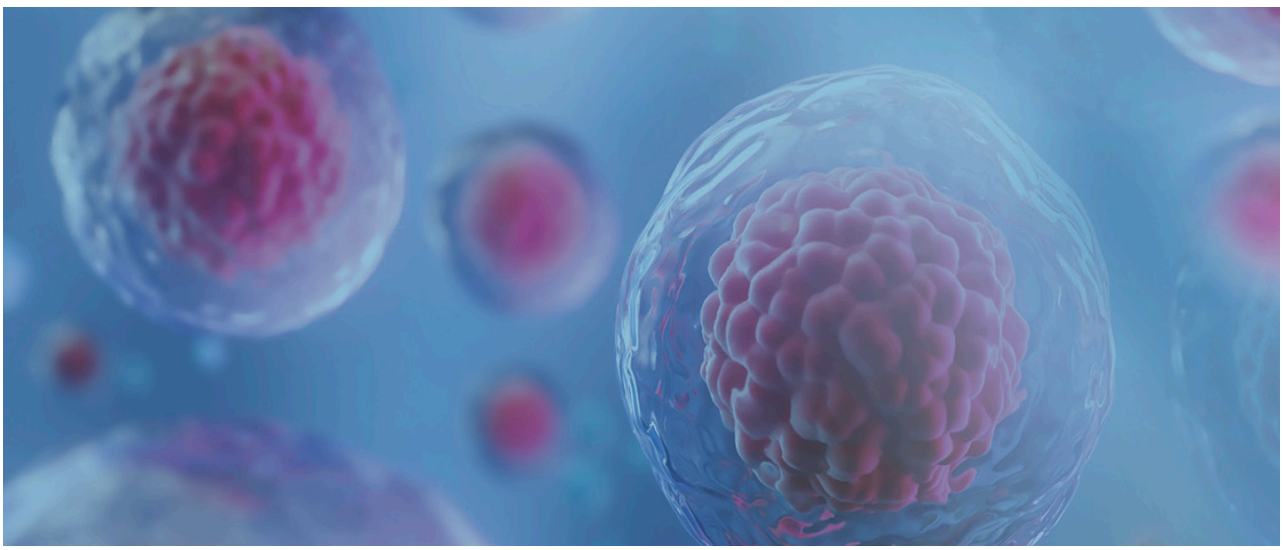
Off-the-Clot from Male AB Donors (OTC)

Off-the-Clot serum is processed from whole blood donations, which are allowed to clot naturally and without the use of anticoagulants. This natural process of clotting separates the serum from the blood cells and clotting factors leaving the liquid portion of blood. OTC may perform better in some cell culture systems due to the natural clotting process and the lack of anticoagulants that are used in the plasmapheresis process.

Additional Applications of Human Serum in Cell Therapy

Other uses of human serum in cell therapy applications include the use of the serum in washing solutions as well as freezing cells. The serum in the wash solution gives the wash solution a buffering capacity as well as nutrients for the cells that allow the cells to maintain viability through the centrifugation and concentrations steps. The use of the serum in freezing media can assist in the transition phase so that DMSO or other freezing components can be used and cells can remain viable through the freezing and thawing process due to the serum proteins.

Summary: **Human male AB serum is very important for cell therapy products due to its utility in the cell proliferation process. By addressing concerns over which type of serum to use and applying this to early-stage clinical development, cell therapy developers can mitigate the risk that would be present if a different serum were chosen which could cause regulators to suggest changes to this critical reagent, risking delays in the clinical development process.**



Regulatory Requirements – Human Serum and Cell Therapy Development

The increasing use of human AB serum and other human-derived serum materials in cell therapy development has opened promising therapeutic avenues but also raised complex regulatory challenges. As the scientific community accelerates the pace of innovation, regulatory frameworks are evolving, and the risk and compliance requirements need to be understood to keep pace.

Understanding the current global regulatory expectations for the sourcing, processing, and use of human serum in cell culture is essential to avoid delays, reduce risk, and ensure patient safety. Failure to anticipate or comply with these expectations has already resulted in delayed IND filings, halted trials, and extensive remediation efforts.

Regulatory Landscape for Use of Human Serum

As cell therapies gain more prominence with growing indications, different geographical regions are expanding the regulatory guidelines for the manufacture and use of these cutting-edge therapies. Regulatory requirements can differ between regions. The different regions are highlighted below.

US Regulations and Guidance

The U.S. Food and Drug Administration (FDA) has a well-established regulatory framework governing human blood and blood-derived components. For developers of cell and gene therapies (CGT), understanding how these apply to ancillary materials such as human serum used in cell expansion is critical.

Key US Regulatory Frameworks:

- **21 CFR Part 640**: Outlines the foundational requirements for collection, processing, and donor eligibility related to human blood and its components. Any facility involved in sourcing serum must meet these standards.
- **21 CFR 610.40**: Mandates comprehensive testing of human blood for transfusion-transmitted infections (TTIs), including HIV, HBV, HCV, West Nile Virus, syphilis, and more. This ensures the baseline safety of any derived material used in manufacturing or R&D.
- **21 CFR 1271:** Governs Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps). While human serum itself may not be classified as an HCT/P, when used in conjunction with live cell cultures for therapeutic development, the donor eligibility and tissue practice requirements outlined in Sections 1271.75, 1271.80, and 1271.85 are directly relevant.
- **Draft Guidance on Human and Animal-derived Materials in the Manufacture of Cell & Gene Therapy Products:** Focuses on key items:
    - **Thorough materials characterization:** Materials should be thoroughly characterized to ensure safety, quality, and identity. This includes understanding the source, processing, and potential contaminants. When using human AB serum in the manufacture of cell therapies, suppliers of human AB serum should anticipate that companies will ask for information related to how the human AB serum was collected, how the product is manufactured and information related to contaminants and other safety concerns.
    - **Risk Assessment:** Manufacturers of human AB serum should conduct risk assessments considering factors like the material's origin, processing methods, and the potential for introducing impurities or pathogens into the final product and what steps have been taken to mitigate these risks.

- **Documentation:** Detailed documentation of material sourcing and risk assessments should be included in regulatory submissions, particularly in the Chemistry, Manufacturing, and Control (CMC) sections of Investigational New Drug (IND) applications. Manufacturers of human AB serum should expect to be able to assist cell therapy developers by supplying critical documentation or supporting them with a drug master file (DMF) if manufacturing is confidential.

- **Transparency and records retention:** It is important that manufacturers of human AB serum document the manufacturing process with potential sources of contamination. The collection of information should start with donor questionnaires, informed consent and health assessment and move through collection, transport, receiving specifications, processing, lot release testing, packaging, storage and shipping.

Summary: **The FDA expects human AB serum suppliers to have the appropriate GMPs implemented with traceable donor history, documented eligibility screening, and viral safety testing—even if the serum is used upstream of final product formulation. Clinical-stage companies have faced FDA delays because they failed to apply this level of rigor to so-called "non-critical" reagents and with the new guidance document, there is increased scrutiny by the FDA when it comes to ancillary materials from human sources.**

EU Regulations and Guidance

In the European Union (EU), human serum is regulated under Directive 2002/98/EC, which establishes safety and quality requirements for human blood and components. Although it excludes HCT/Ps directly, the EMA expects full transparency and validation for all raw materials used in cell therapy manufacturing.

Key EU Expectations:

- **Use of plasma from limited donor pools**, unless sterilization measures such as gamma irradiation are applied.
- **Full traceability of collection and testing**—aligned with GMP principles—even when the material is used upstream.
- **Documentation** showing that material collected for fractionation is not co-mingled with transfusion-grade plasma unless it meets both standards. In recent interactions with the European Medicines Agency (EMA), companies were asked to justify pool sizes and viral inactivation methods used for ancillary materials—even though they were not part of the final drug product. One firm, aiming to accelerate its submission, used pooled serum from over 30 donors without gamma irradiation. The application was delayed pending extensive justification and a post-approval commitment.

Summary Considerations of Global Regulations and Guidance

Each regulatory body has its own approach:

- **UK MHRA** generally aligns with EU directives but has increased scrutiny post-Brexit for documentation and supply chain traceability.
- **Japan PMDA** expects cell therapy developers to show donor testing consistent with local standards and to demonstrate equivalency for foreign-sourced materials.
- **China NMPA** requires that the production of human AB serum comply with NMPA GMPs and the establishment of a comprehensive Quality Management System (QMS). Due to the frequent updating of regulations by NMPA, it is strongly recommended that companies exporting into China consult with regulatory experts and legal counsel.

Global Regulatory Considerations at-a-Glance

To proactively manage regulatory expectations, developers should consider the following when selecting and qualifying human serum:

Criteria	Selecting and qualifying human serum
Collection Country	U.S.-sourced material is often preferred due to existing infrastructure and FDA oversight.
FDA-Registered Collection Centers	Ensures traceability and compliance with 21 CFR 640/1271 requirements.
Donor Travel History	Regulatory bodies expect evaluation for potential exposure to prion diseases and TTIs.
Donor Pool Size	Larger pools increase contamination risk; smaller pools may be mandated unless irradiation is used.
Gamma Irradiation	Mitigates viral contamination but may impact serum performance—requires revalidation.
Adventitious Agent Testing	Routine screening for microbial and viral contaminants must be documented and qualified.
Heat Inactivation	May inactivate complement proteins but does NOT ensure sterility or eliminate viral risk.
Serotype & Demographics	Male AB serum is often preferred to reduce variability due to hormones and mitigate MHC antibody presence.

Lessons Learned in Working with Regulatory Agencies

Success Story

A cell therapy firm preparing for its first pre-approval inspection (PAI) chose to preemptively submit viral inactivation validation data for its human AB serum, even though the agency hadn't formally requested it. The result? The inspector complimented their "proactive compliance approach," and the firm sailed through without a single observation.

Cautionary Tale

Another firm outsourced its serum sourcing to a third-party supplier but failed to audit their documentation systems. During an FDA inspection, it was discovered that donor pool data and testing records were incomplete. The resulting 483 cited "failure to maintain control of ancillary raw materials critical to product development." The firm lost nine months correcting the issue before progressing to Phase 2.

Bottom Line: Don't Treat Human Serum Like Just Another Reagent

Human serum plays a vital role in cell growth, differentiation, and therapeutic potency. Regulatory bodies are increasingly treating it as a critical raw material regardless of how early it enters the process.

Summary:

- Treat human serum as a **regulated input,** not a research material.
- Validate suppliers and request complete documentation.
- Engage regulators early with data and justifications, don't wait to be asked.

Human Serum Manufacturing Considerations

With the advances in CAR-T and other cell therapy treatments, there is a need for specific considerations when evaluating human AB serum, and other ancillary materials used in the manufacture of cell therapies. Cell therapy developers should engage with their human AB serum supplier to assess all aspects of the supplier's quality system, raw material sourcing, and manufacturing processes, as well as general capabilities to support clinical development and commercialization. Considerations for supplier selection can include:

Raw materials collection

For human AB serum, it is important that the collection centers are registered/licensed with the FDA. The donor should undergo a health assessment prior to the donation and fill out a questionnaire. This questionnaire will evaluate health history as well as the travel habits of the donor. An informed consent is required to confirm that the donor understands the process of donating and what it entails. For plasmapheresis procedures, the collection facility should be using equipment that has been approved by the FDA with the appropriate approved disposable sets. Currently, donors living in the United States that have passed questions related to travel are the most appropriate donors.

Donor Unit Testing

Once the collection is obtained, the donation should be tested for adventitious agents. Adventitious agent testing should include, but not limited to, the references in 21 CFR 610.40 and 21 CFR 1271. The table below represents commonly required donor level testing.

Donor Screening Tests	Definition
HBsAg	Hepatitis B Surface Antigen
Anti-HCV	Detects Hepatitis C antibodies
Treponema pallidum	Syphilis
HBV-NAT	Hepatitis B Nucleic Acid Testing
HIV-NAT	Human immunodeficiency Virus Nucleic Acid Testing
HCV-NAT	Hepatitis C Nucleic Acid Testing
West Nile Virus NAT	West Nile Virus Nucleic Acid Testing
Trypanosoma cruzi	Chagas
Anti-HTLV I/II	Human T-lymphotropic Virus type I/II
Anti-HBc IgM	Detects IgM antibodies for Hepatitis B core
Anti-HBc IgG	Detects IgG antibodies for Hepatitis B core
Parvo B19 DNA	Parvovirus B19 strain DNA
HAV RNA	Hepatitis A RNA Testing
Atypical Antibodies	Atypical Antibodies
Anti-HIV 1/2	Detects human immunodeficiency virus type 1/2 antibodies

Testing can be performed on individual samples or pooled samples depending on the requirements set forth in the package inserts of the specific tests. These tests should be approved by the FDA and in the case of European testing, CE marked.

Pooling

The pooling strategy should be assessed depending on the complexity needed for the application. If the human AB serum product is being used for research purposes, then complexity of the pool of donors going into a lot of human serum may not be of concern. However, if the human AB serum product will be used for clinical or commercial applications, then the complexity of the pool is of concern. In certain regions (e.g., European Union) donor pools of limited size should be used. While the specific limitation of the pool is not always defined, some regulatory agencies define limited as less than or equal to 16 donors[6]. If other post processing like gamma irradiation is utilized, then the pool complexity becomes less of a concern. It is the responsibility of the sponsor to define the limited pool size of the human AB serum product.

Defibrination

When using plasma derived serum, one key consideration for cell therapy developers is the type of thrombin used to defibrinate the plasma. The two types of thrombin that are commercially used are bovine thrombin and recombinant human thrombin. Because bovine thrombin is a xenogenic product derived from cows, it may be better suited for human AB serum used in research applications. Additionally, due to the long latency period of bovine spongiform encephalopathies (BSE), there are concerns about the use of bovine-based products for use in human therapies. There are FDA-Approved (for surgical applications) recombinant human thrombin products available (i.e., RECOTHROM®) that are appropriate for the defibrination process for human AB serum. The recombinant human thrombin is used to overcome the presence of anticoagulant that is used as part of the plasmapheresis process and does convert to the fibrin clot which is removed during manufacture of the serum. Consequently, plasma derived serum that is manufactured using recombinant human thrombin is perfectly suited for use in human cell therapy applications.

Filtration

Human AB serum for research and clinical use is processed using filtration methods that remove particulates of a specific size. The filter size which is commonly used is a 0.1 µm pore size. This filter size should be used in triplicate to ensure that all particulates 0.1 µm or larger will be filtered out of the manufactured serum. This pore size is also small enough to filter out mycoplasma species. As a general check of the filtration step, at least the terminal filter should be checked for integrity to ensure that there are no rips or tears in the filter membrane.

Filling

Filling of the human AB serum should be performed under aseptic conditions. To do this, a Grade A or ISO 5 environment is needed so that open manipulations can occur with a negligible risk for aseptic breach. Personnel should be gowned appropriately and should be adequately trained. Media fills and aseptic process simulations (APS) should be performed by the human AB serum manufacturer on a routine basis to demonstrate proficiency in aseptic processing. The manufacturer's APS design should take into account a worst-case stance for all of the processes including container/closure, media preparation and possible interventions.

Release testing

Release testing for the human AB serum product should focus on critical quality attributes (CQA). These CQAs include pH, osmolality, mycoplasma, endotoxin and a biochemistry panel. All of these tests or levels of analytes can impact certain cell culture systems and cell proliferation depending on the sensitivities of the cells to the levels that are present.

Heat Inactivation

The process of heat inactivation (HI) is performed for the sole purpose of inactivating complement in the serum. Complement is a series of proteins in the serum that get activated sequentially when antibodies with immunity interact with antigens. Complement proteins can be harmful to some cells and can have serious effects in cell based systems. By heating the serum to 56^{0}C for 30 minutes, complement is inactivated and the effects negated. One downside that can result from the heating of serum is that proliferation of cells can be decreased due to heat labile proteins becoming denatured. Suppliers should have documented and qualified the heat inactivation processes.

Gamma Irradiation

Gamma irradiation (GI) is a commonly deployed method for achieving serum sterility using radiation (typically cobalt-60) by inactivating the genomic material of adventitious agents, rendering them non-infectious at ≥ 30 kGy. Gamma irradiation tends to be the preferred method as it can be achieved in the final product containers without thawing the product. As the dosing of gamma irradiation goes up, the effectiveness of inactivating viruses also increases. However, there is a downside to increased dosing, as more proteins will get cross-linked, and therefore inactivated, and the performance of the serum and the proliferation of cells may be negatively impacted. Suppliers should have completed gamma irradiation validation studies using their primary and secondary packaging.

Custom manufacturing (custom fills, ready-to-use, etc.)

Many cell therapy developers may desire customization in the manufacturing of their human AB serum products. Examples may include filling a specific quantity of serum into a custom single use cryo-bag; adjusting the volume in the primary container to larger or smaller volumes (e.g., 50 mL, 1,000 mL) to reduce pipetting or waste; or adding a mixture of additives like growth factors into the serum to support specific cell growth. Further, as cell therapies move closer to commercial, many companies want to remove risk in the manufacturing process, and this can include closing a system such that an aseptic breach is less likely. Some suppliers have the capabilities required to collaborate with cell therapy developers to deliver human AB serum in customized formats that address specific manufacturing challenges, which can remove bottlenecks within the cell therapy developer's process.

Quality Management System/Manufacturing Quality System

For ancillary materials that will come into contact with the final product, there is an expected level of quality that should be adhered to for human serum products. These materials should be produced under cGMP conditions in facilities that are operated and maintained to ISO and European standards. Raw materials that are used in the production of the human AB serum should be traceable and should have a level of quality oversight either in the manufacture or receipt of the material (e.g., ISO 13485 certification). The verification steps related to the raw material quality ultimately establish the baseline for final product quality. Requirements for human serum are listed in the Code of Federal Regulations in the United States and other regulatory proceedings in other geographical jurisdictions.

Quality Management System/Supplier Management and Raw Material Supply

Cell therapy developers should assess their human AB serum supplier's QMS specific to the raw material supply. Manufacturers of the human AB serum products should have a good quality system and should conduct comprehensive audits of the vendors of the raw materials and plasma used in their manufacturing processes. These audits should also consider the collection entities if the supplier is distributing the raw material. Audits should confirm that the collection facilities are registered with the FDA and that the collection of the donation, in the case of plasma, is performed on an approved device from the FDA.

Supply Chain Considerations

As more cell therapies advance through clinical development and gain commercial status, the supply of a critical reagent like human serum will start to stress the supply chain depending on the type of raw material that is used for the production of the human serum. There are certain considerations that need to be assessed when choosing the correct type of human serum, including:

- Geographical region for the raw material collection
- Pool size of the manufactured product
- Type of serum

Cell therapy developers using human AB serum should assess the final usage of the material and the target global markets for their therapy. If there is no doubt about where the material will be used, then companies can focus on obtaining human serum raw material from that geographical region. If there is a possibility that the final therapeutic product could be approved and used in a diverse number of global markets, then the company needs to determine what is the correct approach and specifications for the human serum used in their product manufacturing.

Raw Material Origin

The geographical region for the donor is critical for assessing the usability of the donation. Since the late 1980's and early 1990's, there have been restrictions on the use of blood from donors that have traveled or resided in the UK and EU. This is because of the outbreak of transmissible spongiform encephalopathies and bovine spongiform encephalopathies (TSE/BSE) and the long incubation of prions in the infected person. Because the epidemic did not expand to the United States, donors from the United States are preferred by regulatory agencies and cell therapy developers. Donor questionnaires can select out personnel that have traveled to countries where TSE/BSE might have been prevalent.

Plasma Derived Human AB Serum – No Donor Limit

As described in detail above, serum can be obtained from the collection process of plasmapheresis. Plasmapheresis is a major global business that supports a wide range of blood-based products across the healthcare and life science industries. As a result of the extensive plasma collection industry, there is significant global and US supply of raw material for human serum, including male AB serum for support of the cell therapy industry. Given the significant supply base for plasma from male AB donors, human AB serum products manufactured from raw material without donor limitations has a robust and low risk supply chain. However, as discussed below, limitations on donor pool size increases supply chain complexity for plasma derived serum raw material.

Plasma Derived Human AB Serum - Limited Donor Pool

Human AB serum manufactured from raw material pools from a limited number of donors (e.g., ≤ 16) carries more supply chain risk than that of serum manufactured from pools without donor limits simply due to the requirement for multiple donations from the specific donors supporting the pool. FDA regulations allow plasma donors to donate up to two times in a seven-day period, with typical donations from each plasmapheresis donation ranging between 700 and 920 mL. As a result, a pool limited to 16 individual donors requires repeated and sequential donations from each donor to generate raw material in sufficient quantities for manufacturing human AB serum. While the overall plasma collection industry is extensive, the requirement to manage repeated donations from specific donors has the potential to result in supply chain bottlenecks if demand for raw material grows too quickly.

Off-the-Clot

A key consideration for OTC serum is that donors who provide whole blood must wait at least 8 weeks[7] between donations and can donate only up to 6 times per year. As compared to the relative frequency of plasma donations, it is clear to see the potential supply chain bottleneck for OTC raw material simply due to fewer donations per donor. This supply chain risk should be an important consideration to note for cell therapy developers who may find that OTC serum performs better in their processes at small scale. Because of the restrictions around whole blood collection, procuring and processing OTC serum in sufficient quantities to support the volume demands of large target indications for commercial therapeutics has the potential to be exceedingly difficult. Consequently, while OTC serum may demonstrate better cell culture proliferation, it may not be a suitable long-term source of human serum when considering cell therapy applications for indications with a large target population.

Putting in all together – Optimizing Cell Therapy Clinical and Commercial Success

Designing a successful cell therapy program means finding the right balance between cell culture performance, regulatory compliance, supply chain scalability, and long-term commercial feasibility. Each serum selection decision must be established within this broader framework—because the right serum at the research phase may not be viable or optimal for clinical or commercial scale. Mapping out your future plans and aligning with a qualified human AB serum supplier at the earliest opportunity is key to success.

Below is a summary of the strategic recommendations outlined in this whitepaper and are tailored to common goals using human AB serum and incorporating best practices for donor pooling, gamma irradiation, and media optimization.

Cell Culture Performance Optimization

From early-stage programs to commercial operations, where maximizing cell viability, growth, and potency are top priorities, two strong options are:

- Use Off-the-Clot (OTC) human AB serum, gamma irradiated to mitigate regulatory concerns around donor pool size. OTC serum may offer superior performance in some cell lines due to the absence of anticoagulants and its more “natural” clotting profile.
- Use plasma-derived human AB serum from a limited donor pool (≤16 donors) to reduce variability while still adhering to EU and other regulatory preferences for small, controlled donor pools.

This approach ensures high performance in culture systems with tighter control over lot-to-lot consistency and regulatory acceptability.

Regulatory Compliance Optimization

When preparing for regulatory milestones (e.g., IND, BLA, EU clinical trial application), compliance must take precedence:

- Use any type of human AB serum (OTC or PDS) that meets your performance needs but ensure gamma irradiation is applied.
- Gamma irradiation at ≥30 kGy offers documented viral inactivation that addresses EU and U.S. expectations for adventitious agent control and would provide flexibility around donor pool size.

This strategy ensures you’re prepared for scrutiny from FDA, EMA, MHRA, and other global regulators while maintaining manufacturing flexibility.

Scalability and Supply Chain Risk Mitigation

To scale your product to commercial volume and reduce long-term risk:

- Use plasma-derived human AB serum with no donor pool size limitation.
- Plasma can be donated more frequently than whole blood, allowing for higher volumes and more consistent long-term supply.
- Align closely with a qualified supplier on forecasts and update immediately with significant changes in demand.

This approach future-proofs your material sourcing strategy for larger indications and global supply needs.

Balance Across All Considerations

When your objective is to optimize culture performance, compliance, and scalability simultaneously, the most balanced approach is:

- Use gamma-irradiated, plasma-derived human AB serum without a donor pool size limitation, and
- Adjust the media-to-serum ratio to meet the cell culture system's performance requirements.

This model offers a highly scalable, regulator-friendly, and performance-tuned solution for clinical and commercial manufacturing. Serum concentration can be adjusted to offset any minor differences in performance that may arise from using gamma irradiation or broader donor pools, allowing manufacturers to achieve consistency without sacrificing compliance or supply.

Summary:

Each phase of cell therapy development - discovery, clinical, and commercial - demands different priorities. There is no single perfect serum type for all stages, but by understanding the trade-offs and strategies outlined here, developers can make decisions that optimize success across the full product lifecycle.

The goal isn't just to pick a serum - it's to build a system that delivers viable, scalable, and regulatory-compliant therapies consistently to patients.

About GeminiBio

Founded in 1985, GeminiBio has two manufacturing facilities in West Sacramento, California. The company has a 25,000 square foot facility that is dedicated to Animal Origin Free (AOF) upstream and downstream media, buffer and water manufacturing, as well as a 32,000 square foot facility that includes a cGMP warehouse and classified manufacturing suites for Animal Origin (AO) and Xeno Free (XF) products. Both facilities are cGMP, and the company is ISO 13485:2016 certified and an FDA registered Class 1 Medical Device manufacturer.

GeminiBio's facility includes a range of ISO 7 processing suites with ISO 5 production areas, including suites with 500-liter and 1,000-liter single use mixing vessels, and classified manufacturing space with 5,000-liter and 10,000-liter stainless-steel mixing vessels – allowing GeminiBio to support cGMP batch sizes spanning from 10-liters to 10,000-liters. Additional capabilities include aseptic filling into diverse containment types (rigid and flexible) and sizes (500 mL bottles to 1,000-liter pallet tanks). Additionally, the company has segregated ISO 7 processing suites for Animal Origin Free, Animal Origin, as well as Xeno Free products – which includes validated processes for the movement and segregation of raw materials and finished goods.

The company has extensive cGMP warehousing capabilities, including temperature mapped and validated storage conditions at -20C, 2-8C, and controlled room temperature (CRT).

Specific to human serum in the support of cell therapy developers, GeminiBio has a market-leading portfolio of both Research Grade and Clinical Grade products, and capabilities to ensure cell therapy developers can successfully advance their technologies.

Research Grade Products

- GeminiBio offers two research grade products, including Normal Human Serum (100-110-100) and GemCell™ human AB serum (100-512-100). While GemCell™ human AB serum has limited adventitious agent testing to allow for a value-oriented price, the manufacturing processes utilizes recombinant human thrombin to facilitate cell therapy developer's transition to a clinical grade product as appropriate.
- Research products can be heat inactivated and/or gamma irradiated.

Clinical Grade Products

- To meet the varied needs of cell therapy developers, GeminiBio offers three different clinical grades, including Human Serum AB Off-the-Clot (100-318-100), GemCell™ Plus Xeno-Free (100-912-100), and GemCell™ Plus Xeno-Free, World Grade (100-916-100). All our clinical grade products have extensive viral testing at the donor level, and the plasma derived serum products are manufactured with therapeutic grade recombinant thrombin. GemCell™ Plus Xeno-Free, World Grade is manufactured using raw material from 16 or less donors, whereas GemCell™ Plus Xeno-Free is manufactured using raw material without donor limitations.
- Clinical grade products can be heat inactivated and/or gamma irradiated.

Aseptic Assurance System™

- Advanced therapy developers and manufacturers have gravitated to closed systems to reduce contamination risk during manufacturing and streamline their workflow. GeminiBio's clinical grade human AB serum products are now available in our Aseptic Assurance System™ cryo-bags to improve customer's aseptic processes and reduce risk.

Custom Manufacturing

- GeminiBio can custom manufacture to meet customer's unique fill size, containment, or other requirements. In addition, GeminiBio can manufacture media or cell culture supplements containing human serum based on customer's specific formulations and packaging requirements. Our custom manufacturing streamlines customer workflows and improves their overall aseptic processes.

Regulatory Support

- GeminiBio is committed to support cell therapy developers as they progress through the clinical development process, this includes a Drug Master File submitted to the FDA for our clinical grade products, a gamma irradiation validation for all catalog bottle products, direct scientific support, as well as discounted pricing with Compliance Insight, Inc.

About Compliance Insight, Inc.

Founded in 2000, Compliance Insight has grown into a nationally recognized compliance firm serving FDA-regulated industries. With more than 140 colleagues and headquartered in Cincinnati, Ohio, with branch offices in North Carolina and Colorado, we bring over two decades of practical, hands-on regulatory experience to pharmaceutical, biotechnology, CGT, medical device, and clinical research organizations.

What sets us apart is more than geography—it's mindset. We're not just compliance experts; we're problem-solvers, mentors, and strategic partners. When clients call us, it's because something critical needs to get done—right the first time, under scrutiny, and with confidence.

Our success is grounded in core values that define how we operate:

- **Integrity** – We speak the truth, even when it's uncomfortable, because patient safety and regulatory credibility demand it.
- **Excellence** – Every solution we offer is built for durability—not just inspection day, but for long-term operational strength.
- **Partnership** – We embed with our clients, listen before prescribing, and act like part of the team—because we've been the team.
- **Accountability** – We do what we say, follow through on commitments, and hold ourselves to the same standards we ask of our clients.
- **Practicality** – We translate regulatory language into real-world actions. No fluff. No vague theory. Just what works.

Compliance Insight's two primary service pillars: Regulatory Services and Quality Services, reflecting our unique approach, client impact, and value-driven delivery model.

Regulatory Services

At Compliance Insight, our Regulatory Services are designed to support clients throughout the entire product lifecycle—from development through approval and beyond. We bring both strategic insight and tactical execution to help life science organizations navigate complex regulatory pathways with confidence and speed.

Core Regulatory Capabilities Include:

- **Regulatory Strategy Development:** We help clients map out the most efficient path to regulatory approval, including IND, NDA, ANDA, and BLA planning. Our specialists assess data readiness, identify regulatory risks, and ensure submission plans align with evolving FDA expectations.
- **Regulatory Submission Support:** Whether you're preparing your first filing or managing post-market obligations, we provide hands-on expertise in compiling, reviewing, and submitting regulatory documents. We also support eCTD readiness and FDA communication strategy.
- **Pre-Approval Inspection (PAI) Preparation:** We conduct readiness assessments, mock inspections, and team training to ensure that when the FDA arrives, your documentation, personnel, and systems are audit-ready and defensible.
- **FDA Meeting Support:** From pre-IND meetings to post-market interactions, we guide clients through formal and informal FDA communications, including meeting prep, briefing document development, and strategy for response to FDA queries or observations.

- **Regulatory Intelligence & Interpretation:** We monitor, interpret, and apply current regulatory guidances and enforcement trends to help clients stay ahead of what's coming—not just respond to what's happened.

Quality Services

Our Quality Services are built to embed operational excellence into your systems—so you're not just meeting compliance requirements, you're building a culture that sustains it.

Core Quality Capabilities Include:

- **Quality Management System (QMS) Development and Remediation:** We build, assess, and optimize QMS frameworks aligned with 21 CFR Parts 210/211, 820, ATMPs and applicable ICH and ISO standards. Whether designing from scratch or remediating findings, our systems are audit-proof and scalable.
- **Deviation, CAPA, and Change Control Systems:** Our team enhances the effectiveness of your deviation handling and CAPA processes, ensuring root causes are identified and sustainable corrections are implemented and tracked.
- **Internal and Supplier Audits:** We provide independent GMP, GCP, and GLP audits—of your internal systems or third-party suppliers—with risk-ranking and remediation recommendations that are inspection-grade.
- **Training & Cultural Development:** Through our TEACM Method (Train, Educate, Audit, Coach, Mentor), we help build compliance behaviors from the floor to the executive suite—training teams not just on what the regulations say, but how to live them every day.
- **Data Integrity Assessments:** We perform comprehensive reviews of data systems—electronic and paper-based—to ensure they meet FDA expectations for ALCOA+ principles.
- **Inspection Response & 483 Remediation:** When the FDA leaves a mark, we help you respond—strategically, clearly, and fast. We build sustainable remediation plans that don't just satisfy inspectors but restore long-term operational trust.

At Compliance Insight, we don't believe in one-size-fits-all. We believe in customized compliance solutions, grounded in decades of experience, tailored to each client's scale, product type, and regulatory context. From pre-approval inspections to quality system design, from remediation to training and cultural transformation, Compliance Insight delivers value-added compliance services that not only resolve regulatory risk but also elevate how organizations think about quality and regulatory.

We don't just prepare companies for the FDA. We help build companies that the FDA—and their patients—can trust.

Learn more about how we do it at www.compliance-insight.com.

References

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3. Sun et al, Toxicity of silicon dioxide nanoparticles with varying sizes on the cornea and protein cornea as a strategy for therapy, Science Bulletin, volume 63, Issue 14, 30 July, 2018; 907-916

4. LSP-DOC-10273, Human AB serum product sheet, Life Science Production

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Additional Reference Material

Code of Federal Regulation references

- **21 CFR 640** - Additional Standards for human blood and blood products
- **21 CFR 610.40** - Test Requirements
- **21 CFR 1271** - Human cells, tissues, and cellular and tissue based products
- **21 CFR 1271.75**- How do I screen a donor
- **21 CFR 1271.80** - What are the general requirements for donor testing
- **21 CFR 1271.85** - What donor testing required for different types of cells and tissues

Ancillary references

- Draft guidance: Considerations for the Use of Human-and Animal-Derived Materials in the Manufacture of Cell and Gene Therapy and Tissue-Engineered Medical Products
- USP<1043> - Ancillary materials for cell and gene tissue engineered products
- EP5.2.12 - Raw materials of biological origin for the production of cell based and gene therapy medicinal products
- PFSB/ELD Notification No. 1002-1 - Standards for biological raw materials (PMDA)
- EU Directive 2002/98/EC- Setting standards of quality and safety for the collection testing, processing, storage and distribution of human blood and blood components

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