ALLIANCE FOR REGENERATIVE MEDICINE

REGULATORY ANALYSIS

Final Report

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OVERVIEW

The objective of this report is to:

- Identify and assess all FDA, EMA related regulations and/or guidance relevant to cell and gene therapy that are directly relevant to the key areas indicated below; and
- Identify the most significant areas of discrepancies or gaps in the regulations and/or guidance in these topic areas.

The scope of this project is limited to the three priority areas for international regulatory convergence identified by the Alliance for Regenerative Medicine:

1. GMP requirements, including how to phase appropriate cGMP expectations
2. Donor eligibility requirements
3. Long-term follow-up and use of registries for real world evidence generation

DONOR ELIGIBILITY DETERMINATION WORKSTREAM

Regulatory Oversight Related to Donor Eligibility (DE) Determinations

United States

In the United States (US), the Food and Drug Administration (FDA) is the authority responsible for regulation of human cells or tissues intended for implantation, transplantation, infusion, or transfer into a human recipient. These products are referred to as human cells, tissue, and cellular and tissue-based products, or HCT/Ps. FDA applies a tiered, risk-based approach to the regulation of HCT/Ps, where HCT/Ps that meet specific criteria or fall within detailed exceptions are regulated solely under Part 361 of the Public Health Service Act (referred to as “361 HCT/Ps”) and do not require premarket review and approval. All other HCT/Ps are regulated by the FDA under both the Tissue Rules and the applicable drug, biologic, or medical device regulations. Regardless of the regulatory pathway, all HCT/Ps must comply with DE determination requirements, including donor screening and testing, unless they are exempt.

The FDA plays a broad role in overseeing activities related to DE determinations.

- Section 361 of the Public Health Service Act gives the FDA the authority to make and enforce regulations to prevent the introduction, transmission, or spread of communicable diseases. Under this authority, the FDA issued the regulations in Title 21 Code of Federal Regulations (CFR) Parts 1270 and 1271, also referred to as the Tissue Rules, which provide the legal requirements for DE determinations.

- The FDA is the regulatory authority responsible for overseeing HCT/Ps that are regulated solely under Part 361 of the PHS Act, including bone, skin, corneas, ligaments, tendons, dura mater, heart valves, hematopoietic stem/progenitor cells derived from peripheral and cord blood, and reproductive tissues.

- The FDA is the regulatory authority that oversees HCT/Ps that are also regulated as medical devices, drugs or biological products in the investigational and marketing approval/post-marketing stages. As part of their review, the FDA ensures that these products comply with DE requirements.

- As the authority responsible for medical device regulation in the US, the FDA regulates in vitro diagnostic tests used for HCT/P donor testing. These tests are reviewed by FDA’s Center for Biologics Evaluation and Research and are either licensed as biological products under the BLA pathway, or they are cleared (class 2 / 510(k) Premarket notification) or approved (class 3 / Premarket Approval application) under the medical device pathway.

Two other federal agencies play important roles in providing oversight related to DE determinations. The Center for Medicare and Medicaid Services (CMS) is the national authority that regulates all laboratory testing (except research) performed on humans in the U.S. through the Clinical Laboratory Improvement Amendment (CLIA). This includes a laboratory certification process. The Health Resources and Services Administration (HRSA) is the authority that oversees organ transplantation within the US, including bone marrow transplantation.

FDA's DE policies are based upon consideration of risks from the donor and product, and the affect that ineligible donors might have on the supply of human cells and tissues.

Under 21 CFR 1271.50(b), a donor is eligible only if:

> • *Screening shows that the donor is free from risk factors for, and clinical evidence of, infection due to relevant communicable disease agents and diseases, and is free from communicable disease risks associated with xenotransplantation; and*
>
> • *Test results for relevant communicable disease agents are negative or nonreactive, except as provided in § 1271.80(d)(1) for non-treponemal screening tests for syphilis.*

Further specifications regarding DE requirements, including updates to the list of Relevant Communicable Disease Agents and Diseases (RCDADs), are provided in FDA Guidance.

Table 1: List of the most important regulatory references related to donor eligibility determination requirements in the US. A full list of references that informed the analysis is found at the end of the report.

Key References for the United States	
21 CFR part 1271 Subpart C	Donor Eligibility requirements for HCT/Ps
FDA Guidance for Industry Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) August 2007	Provides detailed donor eligibility determination guidelines
Use of Nucleic Acid Tests to Reduce the Risk of Transmission of Hepatitis B Virus from Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products FDA Guidance for Industry, August 2016	Recommends the use of FDA-licensed nucleic acid tests (NAT) in donor testing for hepatitis B virus (HBV) deoxyribonucleic acid (DNA)
Use of Donor Screening Tests to Test Donors of Human Cells, Tissues and Cellular and	Clarifies that FDA does not consider cleared or approved diagnostic tests or pre-

Tissue-Based Products for Infection with Treponema pallidum (Syphilis) FDA Guidance for Industry September 2015	amendment devices (which have not been licensed, approved, or cleared) to be adequate for use in HCT/P donor testing for T. pallidum infection
Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by Human Cells, Tissues, and Cellular and Tissue-Based Products FDA Guidance for Industry March 2016 updated May 2018	Provides recommendations for screening donors for evidence of, and risk factors for, infection with Zika virus (ZIKV)
Use of Nucleic Acid Tests to Reduce the Risk of Transmission of West Nile Virus from Living Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) FDA Guidance for Industry September 2016 corrected May 2017	Provides recommendations for testing living donors for West Nile Virus (WNV) using an FDA-licensed donor screening test
FDA Guidance for Industry Availability of Licensed Donor Screening Tests Labeled for Use with Cadaveric Blood Specimens June 2000	FDA expects that testing of cadaveric samples for HIV-1, HIV-2 and Hepatitis B should be performed using test kits specifically labeled for screening of cadaveric blood specimens
Revised Recommendations for Determining Eligibility of Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products Who Have Received Human-Derived Clotting Factor Concentrates FDA Guidance for Industry November 2016	Contains information on infectious-disease risks related to receipt of FDA licensed human-derived clotting factor concentrates
FDA website: Donor Eligibility Final Rule and Guidance Questions and Answers https://www.fda.gov/vaccines-blood-biologics/tissue-tissue-products/donor-eligibility-final-rule-and-guidance-questions-and-answers	FDA Q&A related to the donor eligibility rule

FDA website: Testing HCT/P Donors for Relevant Communicable Disease Agents and Diseases https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/testing-hctp-donors-relevant-communicable-disease-agents-and-diseases	List of FDA cleared/approved/licensed HCT/P donor tests

European Union

Unlike in the US where oversight is largely consolidated under the FDA, in the European Union (EU) regulatory oversight of human tissue and cell therapies, and the associated DE determination activities, is divided across many different regulatory bodies.

The general quality and safety provisions covering donation, procurement, testing, processing, preservation, storage and distribution of human cells and tissue intended for human applications, and of manufactured products derived from human tissues and cells intended for human applications, are primarily covered in the EU Tissue and Cells Directives consisting of a Parent Directive (2004/23/EC) and two technical Directives (2006/17/EC & 2006/86/EC). Therapies derived from blood and blood components may, as an alternative, comply with the applicable standards of quality and safety for the collection and testing of human blood and blood components found in Directive 2004/33/EC, implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components.

When adopting a Directive into national law, a member state is free to change the format and content of the directive; however, the intended results of the directive must be achieved. As a result, the EU Tissues and Cells directives establish minimum requirements for DE determinations. Member states may establish more stringent requirements.

Member states are responsible for designating a National Competent Authority (NCA) for human tissue and cell regulation. According to Directive 2004/23, all tissue establishments where activities of testing, processing, preservation, storage, or distribution of human tissues and cells intended for human applications are undertaken must be accredited, designated, authorised, or licensed by an NCA for those activities. The designated NCA in each member state inspects tissue establishments for compliance with applicable laws and requirements, including their DE determination procedures.

The NCAs for tissues and cells for each member state are listed in Appendix A. For example, in the United Kingdom (UK) the Human Tissue Authority (HTA) is the designated NCA responsible for ensuring that the removal, storage and use of tissue and organs (other than gametes and embryos) is undertaken safely, ethically and with proper consent.

Similar to the US approach, the EU applies a tiered, risk-based approach to the regulation of human tissues and cellular therapy products. Higher risk tissue and cell-based therapies are regulated as advanced therapy medicinal products (ATMPs). An ATMP may be a gene therapy medicinal product, somatic cell therapy medicinal product, tissue engineered product, or a combination of two or more of these products. Human Cells and Tissues Directive 2004/23/EC, as implemented by Commission Directive 2006/17/EC, also applies to the donation, procurement, and testing processes for cells and tissues regulated as ATMPs; all further aspects are covered under the ATMP Regulation. Along the same lines, when a product is both an ATMP and a human tissue or cell product, the donation, procurement, testing and any initial processing steps that are performed at a tissue bank (such as the derivation of a master cell bank) fall under the national human tissue regulatory authority; subsequent manufacturing steps fall under the regulatory authorities for ATMPs.

The designated NCA for ATMP regulation is often different from the NCA for human tissue and cells. For example, in the UK, the Medicines and Healthcare Products Regulatory Agency (MHRA) is the NCA for ATMP regulation and is responsible for clinical trial authorisations and other activities such as performing facility inspections. Furthermore, ATMPs are subject to the European Medicines Agency's (EMA) centralized Market Authorization Application procedure for achieving marketing approval. A further complication is that blood based starting materials are overseen by the regulatory authority for blood and blood products, such as the MHRA in the UK.

In addition to these regulatory authorities, transplantation-related activities at the Council of Europe are co-ordinated by the European Directorate for the Quality of Medicines & Health-Care (EDQM). This Directorate is a key European organisation involved in the harmonisation, co-ordination, standardisation, regulation and quality control of medicines, blood transfusion, organ transplantation, pharmaceuticals, pharmaceutical care, consumer health, cosmetics and food packaging.

Regarding the regulation of donor testing, in vitro diagnostic (IVD) tests used in human cell and tissue donor testing are regulated as IVD medical devices in the EU. They are CE-marked by notified bodies and are subject to oversight by the designated medical device NCA and the European Commission. Laboratories that perform donor testing are certified, licensed or accredited by national authorities such as the United Kingdom Accreditation Service (UKAS) in the UK.

This is a complex system of regulatory oversight and cross-agency communication and coordination is essential.

Table 2: List of the most important regulatory references related to donor eligibility determination requirements in the EU. A full list of references that informed the analysis is found in at the end of the report.

Key References for the European Union	
Directive 2004/23/EC	Requirements for the donation, procurement, testing, preservation, storage and distribution of human tissues and cells intended for human use
Commission Directive 2006/17/EC amended in 2012 by Commission Directive 2012/39/EU	Requirements for the procurement of human tissues and cells, selection criteria for donors of tissues and cells, laboratory tests required for donors, tissue and/or cell donation, procurement and reception procedures at the tissue establishment and requirements for direct distribution to the recipient of specific tissues and cells
Guide to the quality and safety of tissues and cells for human application, European Committee (Partial Agreement) on Organ Transplantation (CD-P-TO), EDQM, 3rd edition, 2017	Provides non-binding recommendations and technical guidance on ensuring the quality and safety of human tissues and cells applied to patients

Summary of Differences Between the US and the EU DE Regulations

For our analysis, we compared the regulatory requirements contained in the references listed in tables 1 and 2, for the US and EU respectively, and we identified the following differences:

Factor	Impact
1. US donor screening for Variant Creutzfeldt-Jakob Disease (vCJD) risk excludes most Europeans from HCT/P donation	HIGH
2. Disease-specific donor testing requirements are not harmonized	HIGH
3. In the US, you must use donor tests that are approved, cleared or licensed by the US FDA	HIGH
4. FDA requires donor screening for Zika Virus	HIGH
5. In the US, testing laboratories must be CLIA certified	HIGH
6. In the EU, all records pertaining to traceability must be retained for 30 years	HIGH
7. The EU has repeat donor sampling and serology requirements for living donors	MEDIUM
8. In the EU, autologous donors are not exempt from DE determinations	LOW
9. In the EU, donor consent is an explicit part of the DE process	LOW

Impact Rating Scale

HIGH: has the potential to prevent a cell line from qualifying for use in either the US or EU unless an alternative or exemption is granted.

MEDIUM: unlikely to prevent a cell line from qualifying for use but carries other significant implications for the time and cost associated with the development of the therapy across the US and EU.

LOW: unlikely to cause significant time delays or increase the cost of development.

US donor screening for Creutzfeldt-Jakob Disease (CJD) risk excludes most Europeans from HCT/P donation

Creutzfeldt-Jakob disease (CJD) is a rare, degenerative, fatal brain disorder within the transmissible spongiform encephalopathy (TSE) or prion family. CJD is transmissible through cell and tissue transplantation procedures. There are no FDA-approved HCT/P donor screening tests for CJD; the risk of CJD transmission by HCT/P transplantation must be managed through donor screening measures. This involves reviewing a donor's relevant medical records and asking questions about a donor's medical history and relevant social behavior, then determining donors who exhibit conditions or behaviors that increase their risk of disease ineligible[1].

The FDA's Donor Eligibility Guidance provides a list of conditions and behaviors that increase a donor's relevant communicable disease risk, including eight factors that are designed to screen for CJD and variant CJD[1]:

1. *Persons who have been diagnosed with vCJD or any other form of CJD.*
2. *Persons who have been diagnosed with dementia or any degenerative or demyelinating disease of the central nervous system or other neurological disease of unknown etiology.*
3. *Persons who are at increased risk for CJD. Donors are considered to have an increased risk for CJD if they have received a non-synthetic dura mater transplant, human pituitary-derived growth hormone, or have one or more blood relatives diagnosed with CJD.*
4. *Persons who have a history of CJD in a blood relative (with certain exceptions).*
5. *Persons who spent three months or more cumulatively in the United Kingdom (U.K.) from the beginning of 1980 through the end of 1996.*
6. *Persons who are current or former U.S. military members, civilian military employees, or dependents of a military member or civilian employee who resided at U.S. military bases in Northern Europe (Germany, Belgium, and the Netherlands) for 6 months or more cumulatively from 1980 through 1990, or*

[1] FDA Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), FDA/CBER, August 2007, Pages 18-19

elsewhere in Europe (Greece, Turkey, Spain, Portugal, and Italy) for 6 months or more cumulatively from 1980 through 1996.

7. *Persons who spent 5 years or more cumulatively in Europe from 1980 until the present (note this criterion includes time spent in the U.K. from 1980 through 1996).*

8. *Persons who received any transfusion of blood or blood components in the U.K. or France between 1980 and the present.*

The last four CJD/vCJD risk factors directly impact donations by donors with a history of residence in Europe; in particular, the exclusion of persons who spent 5 years or more cumulatively in Europe from 1980 until the present excludes the majority of European donors from making US HCT/P donations.

The quantitative risk assessment that supports the HCT/P donor eligibility determination policy was made publicly available in a draft document entitled "Guidance for Industry: Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)" dated June 2002. The FDA requested input on the policy, stating:

> *"Because there is no readily available demographic information about the HCT/P donor population, FDA encourages establishments to submit with their comments study data concerning the effect that implementation of these recommendations could have on the HCT/P supply."*[2]

While this 2002 draft guidance was never finalized, the recommendations were later incorporated into the FDA Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), released February 28, 2007. There is no publicly available quantitative risk assessment supporting the HCT/P CJD/vCJD donor eligibility policy other than the analysis found in the 2002 draft guidance.

There is a similar CJD policy in place regarding donor deferrals for donors of whole blood and blood components intended for transfusion and source leukocytes. The quantitative risk

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[2] Federal Register Notice: Draft "Guidance for Industry: Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps);" Availability 06/25/2002, 67 FR 42789 pages 42789-42790, Docket No. 02D-0266

assessment supporting the blood donor deferral policy is explained in final FDA Guidance as follows:

> *"BSE has been detected in many European countries. Food chain control measures (and their enforcement) have varied in Europe and cannot be assured for all time periods in question. Because of these uncertainties and the evolving BSE epidemic, donor deferrals on a country-by-country basis have not been practical. Therefore, FDA developed a uniform recommendation for donor deferral based on exposure in Europe outside of the U.K. The highest prevalence of BSE that has been observed in a European country with a strong surveillance program (Switzerland) is approximately 1.5% of the BSE prevalence that was observed for the U.K. between 1980 and 1996. Also, as noted in Section III.B above, residents in France may have consumed at least 5% of their total beef as imported British beef during the epidemic period, while other Europeans almost certainly consumed less. Therefore, the estimated maximum risk of BSE exposure in Europe was taken to be approximately 1.5-5% of that in the U.K. Assuming a "worst-case" relative risk of 5% per day of exposure, a European donor deferral of five years (60 months) was equivalent to a three-month deferral for cumulative travel or residence in the U.K. This remains the basis for our current recommendation to defer donors of Whole Blood and blood components intended for transfusion and Source Leukocytes who have a history of five or more years of residence or travel in Europe outside of the U.K."*[3]

In December 2017 the FDA issued a draft guidance proposing a revised blood donor deferral policy that recommends deferral only for donors who spent time in U.K., Ireland, and France (and donors exposed to U.K. beef on certain U.S. military bases in Europe) and no longer recommending deferrals for time spent in all other European countries. Further, it should be noted that this donor deferral policy does not apply to plasma derivatives, which have a lower risk of vCJD transmission due to the manufacturing steps employed and have greater supply constraints. Plasma derivatives must carry a warning regarding vCJD risks in their labeling.

Impact Level: HIGH

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[3] US FDA Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Products; May 2010 / Updated 2016

This policy has the potential to prevent an allogenic cell line derived in Europe from qualifying for use in the US unless an alternative or exemption is granted by FDA.

Disease-specific testing requirements are not harmonized

Comparing the requirements contained in the FDA regulatory references listed in Table 1 to the requirements contained in the EDQM and the Human Cells and Tissues Directive, we found differences in the disease-specific testing requirements between the US and EU outlined in Table 3 below.

Table 3: Differences in disease-specific testing requirements

RCDAD	US FDA	EDQM	Directive 2006/17/EC, as amended
HIV-1	(1) FDA-licensed screening test either for anti-HIV-1 or combination test for anti-HIV-1 and anti-HIV-2 and (2) FDA-licensed screening NAT test for HIV-1, or combination NAT	The minimum requirement for donor testing for viral infectious agents is antibody detection for HIV 1/2, HBV, HCV and human T-cell lymphotropic virus (HTLV-1; when indicated), plus detection of antigen for HBV. Because NAT assays are more sensitive, and deceased donors cannot be retested after 6 months, serious consideration should be given to also carrying out NAT tests for HIV, HBV and HCV.	Anti-HIV-1,2
HIV-2	FDA-licensed screening test either for anti-HIV-2 or combination test for anti-HIV-1 and anti-HIV-2		Anti-HIV-1,2
HBV	(1) HBsAg, (2) total anti-HBc (IgG and IgM) and (3) NAT test for HBV		HBsAg, Anti HBc
HCV	(1) FDA-licensed screening test for anti-HCV and (2) FDA-licensed screening NAT test for HCV, or combination NAT		Anti-HCV-Ab
WNV	As discussed in the 2007 Donor Eligibility Guidance, FDA determined WNV to be a relevant communicable disease agent or disease in accordance with 21 CFR 1271.3(r)(2). This determination was based on the severity of the effects of WNV, its incidence and prevalence in the donor population, the potential for transmission of WNV by HCT/Ps, and the availability of appropriate screening	Additional test that may be considered depending on the donor's history	Not specifically mentioned

	measures. Testing requirements: For establishments located within the United States (includes the 50 states and District of Columbia), we recommend performing WNV testing (NAT) on HCT/Ps recovered from June 1st through October 31st every year. For all other establishments not specified above, and intending to import HCT/Ps into the United States, testing of HCT/P donors for WNV should be performed year-round.		
HTLV I and II	For donors of viable, leukocyte-rich HCT/Ps: FDA-licensed screening test for anti-HTLV I/II	Testing for HTLV-I antibodies must be undertaken for donors living in or originating from high-prevalence areas, or with sexual partners originating from those areas, or if the donor's parents originate from those areas	HTLV-I antibody testing must be performed for donors living in, or originating from, high-prevalence areas or with sexual partners originating from those areas or where the donor's parents originate from those areas
CMV	For donors of viable, leukocyte-rich HCT/Ps: FDA-cleared screening test for anti-CMV (total IgG and IgM)	Additional test that may be considered depending on the donor's history	Additional test that may be considered depending on the donor's history

Impact Level: HIGH

Because the US guidelines are more stringent, these differences in testing requirements could prevent an allogenic cell line derived in Europe from qualifying for use in the US unless an alternative or exemption is granted by the FDA.

In the US, a sponsor must use donor tests that are approved, cleared or licensed by the US FDA

As stated in FDA Guidance: *"In the Federal Register of July 29, 1997 (62 FR 40429), FDA published a final rule on human tissue intended for transplantation. The final rule, which became effective on January 26, 1998, requires that donor specimens be tested and found negative for the communicable disease viruses: HIV-1, HIV-2, Hepatitis B, and Hepatitis C, using FDA licensed donor screening tests in accordance with manufacturers' instructions. Specifically, 21 CFR 1270.21(d) states that "FDA licensed screening tests labeled for cadaveric specimens must be used when available."*[4]

This is interpreted by the FDA as follows: *"you must use appropriate FDA licensed, approved or cleared donor screening tests, if such tests are available, in accordance with the manufacturer's instructions to perform donor testing. For cadaveric donations, you must use a donor screening test specifically labeled for cadaveric specimens instead of a more generally labeled donor screening test when applicable and when available."*[4]

The EDQM recommends a more flexible policy: *"The tissue establishment should ensure that the laboratory is competent to perform this work and is using appropriate assays and procedures (ideally, with kit designed for donor screening rather than for confirming a diagnosis)."*[5]

The FDA's more specific requirement to use only FDA approved, cleared or licensed tests impacts tissue establishments that rely on HCT/P donor testing performed outside of the US, where other test kits may be available. The FDA requires establishments that have used other tests to apply for an alternative or exemption according to the process in 21 CFR 1271.155. This policy particularly impacts developers of regenerative medicine products that are derived from allogeneic cell lines established outside of the US.

For establishments that wish to comply with the US requirements and that will purchase their test kits in Europe, Table 4 lists the tests that are both FDA licensed, cleared or approved and CE marked in the EU. Although there are no gaps, in several cases, there is only one CE-

[4] FDA Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), FDA/CBER, August 2007
[5] Guide to the quality and safety of Tissues and Cells for human application, European Committee (Partial Agreement) on Organ Transplantation (CD-P-TO), EDQM, 3rd Edition, 2017

marked donor screening test that is also FDA- licensed, cleared or approved for HCT/P donor testing.

It should be noted that, without upfront planning and discussions with donor testing laboratories, other tests could be used. In the EU, there are many other CE-marked infectious disease tests available commercially that are not FDA licensed, cleared or approved for HCT/P donor testing. Secondly, in the US, there are other infectious disease tests that are FDA licensed, cleared or approved for blood donor testing only; those should not be used for HCT/P donors. In the EU, there is no distinction between blood donor tests and HCT/P donor tests in the EDQM or the Directives.

Table 4: A limited number of the FDA licensed, cleared or approved donor tests are also CE marked in the EU

RCDAD	Test Type	FDA cleared/approved/licensed tests that are also CE marked
HBV	HBsAG	Abbott Prism HBsAg Assay
	HBcore	ABBOTT PRISM HBcore
	NAT	Procleix Ultrio and Procleix Ultrio Plus (Girfols), COBAS TaqScreen MPX Test (Roche)
HCV	anti-HCV	Abbott PRISM HCV
	NAT	Procleix Ultrio and Procleix Ultrio Plus (Girfols), COBAS TaqScreen MPX Test (Roche)
HIV-1	anti-HIV-1	Abbott HIVAB HIV-1/ HIV-2 (rDNA) and ABBOTT PRISM HIV O Plus
	NAT	Procleix Ultrio and Procleix Ultrio Plus (Girfols), COBAS TaqScreen MPX Test (Roche)
HIV-2	anti-HIV-2	Abbott HIVAB HIV-1/ HIV-2
HTLV I and II	anti-HTLV I/II	ABBOTT PRISM HTLV-1/HTLV-II Assay, Avioq HTLV I/II Microelisa System
CMV	anti-CMV	Immucor Capture - CMV
WNV	NAT	Procleix WNV Assay (Grifols), Cobas TaqScreen West Nile Virus Test (Roche)
T. Pallidum	Treponemal	ASI TPHA Test (Arlington Scientific), CAPTIA TM Syphilis(T. Pallidum)-G (Trinity Biotech), TPHA Screen (Immucor)
	Non-Treponemal	ASiManager-AT (Arlington Scientific)

Impact Level: HIGH

This policy has the potential to prevent an allogenic cell line derived in Europe from qualifying for use in the US unless an alternative or exemption is granted by FDA.

FDA requires donor screening for Zika Virus

As new diseases emerge, the FDA updates the list of relevant communicable disease agent or diseases (RCDADs) by issuing guidance documents that supplement the recommendations contained in “Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)”. In March 2016, the FDA determined that Zika Virus is a RCDAD for HCT/Ps and added donor screening measures aimed at preventing Zika Virus transmission in a Guidance for Industry. The FDA’s guidance was later updated in May 2018.[6]

In the EU, there are no specific requirements to screen donors for risk factors related to Zika Virus. Testing for the presence of Zika Virus is an additional test that may be considered depending on the donor’s history.[7]

RCDAD	US FDA	EDQM	Directive 2006/17/EC, as amended
ZKV	FDA has identified ZIKV as a relevant communicable disease agent or disease (RCDAD) under 21 CFR 1271.3(r)(2). Appropriate screening measures have been developed for ZIKV, such as review of medical and travel history (discussed in section IV. of this document). Appropriate testing measures to prevent the transmission of ZIKV through HCT/Ps are not currently available. Although nucleic acid tests (NATs) for donor screening are available, they are not considered appropriate for preventing transmission of ZIKV through HCT/Ps. The currently available NATs are designed to detect ZIKV RNA in plasma isolated from a donor blood specimen. ZIKV is readily detected in HCT/Ps, such as semen and umbilical cord blood or other gestational tissues, after viral RNA is no longer detectable in plasma; therefore, blood plasma NAT alone is not sufficient to	Additional test that may be considered depending on the donor's history	Not specifically mentioned

[6] FDA Guidance for Industry: Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by Human Cells, Tissues, and Cellular and Tissue-Based Products, March 2016 Updated May 2018.

[7] Guide to the quality and safety of Tissues and Cells for human application, European Committee (Partial Agreement) on Organ Transplantation (CD-P-TO), EDQM, 3rd Edition, 2017

	determine whether a donor's HCT/Ps may be infected with ZIKV		

Impact Level: HIGH

This policy has the potential to prevent an allogenic cell line derived in Europe from qualifying for use in the US unless an alternative or exemption is granted by FDA.

In the US, HCT/P donor testing laboratories must be CLIA certified

In accordance with the Donor Eligibility Guidance, establishments that perform HCT/P donor testing must be certified to perform such testing on human specimens either under the Clinical Laboratory Improvement Amendments (CLIA) or they must meet equivalent requirements as determined by the Centers for Medicare and Medicaid Services. Examples of the latter include laboratories that have been accredited by accrediting organizations approved by CMS, such as state programs.[8]

The US Centers for Medicare & Medicaid Services (CMS) regulates all laboratory testing (except research) performed on humans in the US under CLIA. Congress passed CLIA in 1988 to establish quality standards, strengthen Federal oversight of clinical laboratories, and ensure the accuracy and reliability of patient test results in response to deaths from inaccurately read pap smears and proliferation of "black box" diagnostic technology with no oversight in physician's offices.

Under CLIA, any facility performing examinations of human specimens (e.g., tissue, blood, urine, etc.) for diagnosis, prevention, or treatment purposes must be:

> *Certified to perform such testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988 (42 U.S.C. 263a) and 42 CFR part 493; or*
>
> *Meet equivalent requirements, as determined by the Centers for Medicare and Medicaid Services (CMS).*[9]

The CMS/CLIA certification process consists of the following steps:

- Complete Form CMS-116.
- Pay applicable fees based on the type of certification.
- Be surveyed, if applicable.
- Meet CLIA certification standards.
- Comply with proficiency testing (PT) requirements: Laboratories conducting moderate and high complexity testing must participate in PT for certain tests. A CMS-approved PT

[8] FDA Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), FDA/CBER, August 2007

[9] CMS website: Brochure: CLIA PROGRAM AND MEDICARE LABORATORY SERVICES fact sheet, https://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNProducts/Downloads/CLIABrochure.pdf
Accessed 6/25/2019

program sends laboratories a set of PT samples approximately three times a year and evaluates the accuracy of the results.[10]

Some laboratories located outside of the US are CLIA-certified. Any testing of materials from human specimens collected in the United States and its territories is subject to CLIA regulations. If specimens are transported outside of the United States for testing by international laboratories, then these laboratories are also subject to the CLIA regulations; they need to be certified for the specific tests performed on US patient samples.[11]

In the EU, by contrast, the EDQM recommends that "evidence should be available to show that any laboratory used for testing of donor samples has been accredited, designated, licensed and/or authorized by the appropriate authority to carry out such testing." This more flexible recommendation allows laboratories that have been accredited in accordance with national requirements to be used for HCT/P donor testing.[12]

Impact Level: HIGH

This policy has the potential to prevent an allogenic cell line derived in Europe from qualifying for use in the US unless an alternative or exemption is granted by FDA.

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[10] CMS Website: How to Apply for a CLIA Certificate, Including International Laboratories https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/How_to_Apply_for_a_CLIA_Certificate_International_Laboratories.html Accessed: 6/25/2019

[11] A searchable database of CLIA-certified labs is located on the CMS website here: https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/CLIA_Laboratory_Demographic_Information.html

International labs can be viewed by selecting state = "FN". A search performed on 6/23/2019 yielded 60 CLIA-certified laboratories that are located outside of the US; 25 of these labs are located in Europe with the largest number found in Germany (Appendix B).

[12] Guide to the quality and safety of Tissues and Cells for human application, European Committee (Partial Agreement) on Organ Transplantation (CD-P-TO), EDQM, 3rd Edition, 2017

In the EU, all records pertaining to traceability must be retained for 30 years

In the EU, organisations responsible for human application (ORHAs) are required to maintain traceability records from the point of receipt of the tissue until 30 years after clinical use or other final disposal. Records that describe procurement, donor testing, processing, storage, distribution and end use are among those that should be retained for 30 years.[13]

The US requires a shorter record retention period. Under 21 CFR 1271.55(d)(4), you must retain records pertaining to a particular HCT/P for at least 10 years after the date of its administration. This includes records created by laboratories performing donor eligibility testing (21 CFR 1271.55(d)).

Impact Level: HIGH

Human cell and tissue facilities in Europe must establish and maintain policies and procedures that allow for an extended record retention period.

[13] Guide to the quality and safety of Tissues and Cells for human application, European Committee (Partial Agreement) on Organ Transplantation (CD-P-TO), EDQM, 3rd Edition, 2017

The EU has repeat donor sampling and serology requirements for living donors

In the EU, re-tests of samples from living donors are required when the collected human cells or tissues are meant for allogeneic use. As stated in the EDQM Guide:

> *Repeat sampling and serology testing is required after 180 days, unless any of the following specific exemption criteria are met. If samples from a living donor undergo serology testing and are also tested by molecular tests (i.e. NAT) for HIV, HBV and HCV, re-testing after a time interval is not required. Because molecular testing can increase sensitivity in the detection of recently acquired infections, molecular testing of all donors using this technology is highly recommended as standard practice. Other circumstances where re-testing a living donor is not required include: 1) if the tissue/cells have been processed using an inactivation step that has been validated for the virus(es) concerned; and, 2) if the tissue/cells will not be stored longer than 180 days prior to use.*[14]

In the US, there are no repeat sampling and serology testing requirements for living donors; however, it should be noted that NAT tests are required as part of donor testing to detect HIV-1, HBV and HCV.

Impact level: MEDIUM

Most cell lines derived in accordance with US requirements will not be subject to this re-testing requirement due to the mandatory use of NAT testing technology for detection of HIV, HBV and HCV; therefore, this discrepancy is lower impact.

[14] Guide to the quality and safety of Tissues and Cells for human application, European Committee (Partial Agreement) on Organ Transplantation (CD-P-TO), EDQM, 3rd Edition, 2017, page 90

In the EU, autologous donors are not exempt from DE determinations

In the US, you are not required to make a determination of donor eligibility or to perform donor screening and testing if the cells and tissues are intended for autologous use.

In the EU, the EDQM states:

> *For cells and tissues for autologous use, eligibility for donation is evaluated on an individual basis, taking into consideration the possible complications and benefits. It is a general rule that harm to the patient should be minimal during the donation process. If the procured tissues or cells will be processed and/or stored, screening for the same biological testing must apply as for an allogeneic living donor, although the results are not necessarily a contraindication for autologous donation as long as procedures are in place to avoid cross-contamination with other processed/stored tissues or cells.*[15]

With regards to testing of autologous samples, the EDQM states:

> *For autologous donors, if the removed tissues or cells are stored or cultured, they must undergo the same serological tests as for allogeneic donors before they can be transplanted back into the donor. If an autologous donor's blood sample has not been appropriately tested or if a test is positive for a relevant infectious disease, this will not necessarily prevent the tissues or cells, or any product derived from them, from being stored, processed and re-implanted in the autologous donor; but this is only true if appropriate storage can provide isolation/segregation to ensure there is:*
>
> - *no risk of cross-contamination with stored allografts;*
> - *no risk of contamination with adventitious agents;*
> - *avoidance of mix-ups due to misidentification*

[15] Guide to the quality and safety of Tissues and Cells for human application, European Committee (Partial Agreement) on Organ Transplantation (CD-P-TO), EDQM, 3rd Edition, 2017, page 72

SOPs based on risk analyses must be in place to define the criteria for acceptance and rejection for contaminated autologous tissues and cells, or if the autologous donor has not been tested for infectious diseases.[16]

Impact level: LOW

This discrepancy can be addressed by introducing appropriate autologous donor testing procedures and therefore it is less impactful on cell therapy development programs.

In the EU, donor consent is part of the donation process

In the EU, informed consent is required for either an allogeneic or an autologous donation as part of the donor recruitment and evaluation process.[17] Informed consent must be given in advance of accepting a donation. The informed consent process must ensure that the donor fully understands the risks and consequences of the donation procedure and the final use that will be given to their donated material.

In the US, DE determination requirements and informed consent requirements are separate; the requirement for informed consent is found in 21 CFR Part 50 - Protection of Human Subjects and applies to all clinical investigations regulated by the FDA. Informed consent is required when involving a human being as a subject in research studies.

Impact level: LOW

This discrepancy can be addressed by introducing appropriate informed consent procedures and therefore it is less impactful on cell therapy development programs.

[16] Guide to the quality and safety of Tissues and Cells for human application, European Committee (Partial Agreement) on Organ Transplantation (CD-P-TO), EDQM, 3rd Edition, 2017, page 90
[17] Guide to the quality and safety of Tissues and Cells for human application, European Committee (Partial Agreement) on Organ Transplantation (CD-P-TO), EDQM, 3rd Edition, 2017, page 232

GOOD MANUFACTURING PRACTICES WORKSTREAM

Summary of Differences Between the US and the EU cGMP Regulations

For our analysis, we compared the regulatory requirements contained in the references listed in tables 5, for the US and EU respectively, and we identified the following differences:

Factor	Impact
1. Timing and extent of GMP implementation	HIGH
2. In the EU, a Potency Assay with Acceptance Criteria is required for Ph1/FIH trials	HIGH
3. In the EU, a Qualified Person must ensure GMP compliance and authorizes FP release	HIGH
4. US Cleanroom Air Classification Standards differ from European Guidelines	HIGH
5. In the EU, the QP must oversee that imported drug products are re-tested for batch certification	MEDIUM
6. Instruments, container closure systems and delivery devices are regulated under the medical device pathways which differ regionally	MEDIUM
7. In the US, GM-cell therapy FP must be tested for RCR, whereas in the EU RCR testing of the vector starting material may suffice	LOW
8. In the EU, living cells, even if their function is mostly structural/mechanical, cannot be classified as devices	LOW

Impact Rating Scale

HIGH: significant difference that could result in phase appropriate GMP/CMC that is designed to meet the requirements for one region failing to meet the requirements of the other region.

MEDIUM: carries other significant implications for the time and cost associated with the development of the therapy across the US and EU.

LOW: unlikely to cause significant time delays or increase the cost of development.

Table 5: List of key regulatory references reviewed for the analysis of differences related to cGMP requirements for ATMP in the US and the EU

US Document Sources
Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs). April 2008
Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products. June 2015
cGMP for Phase 1 Investigational Drugs. July 2008
INDs for Phase 2 and Phase 3 Studies Chemistry, Manufacturing, and Controls Information. May 2003
Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up. July 2018
Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs). July 2018
Potency Tests for Cellular and Gene Therapy Products. January 2011
Comparability Protocols for Human Drugs and Biologics. April 2016
Compliance Program Guidance Manual Chapter – 45 Biological Drug Products. Inspection of Biological Drug Products (CBER). October 2010
EU Document Sources
Draft Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials. Doc. Ref. EMA/CAT/852602/2018

EudraLex, The Rules Governing Medicinal Products in the European Union: Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products. Adoption by the European Commission 22 November 2017
EudraLex, The Rules Governing Medicinal Products in the European Union: Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products. Annex I
Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells. Doc. Ref. EMA/CAT/GTWP/671639/2008 Rev. 1 (26 July 2018)
Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced therapy medicinal products
Guideline On Human Cell-based Medicinal Products. Doc. Ref. EMEA/CHMP/410869/2006
Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products. Doc. Ref. EMEA/CHMP/SWP/28367/07 Rev. 1

Timing and extent of GMP implementation

The EU and the US use two different, and not fully compatible approaches, to lessen the burden of medicinal product development

In the EU full GMP compliance is required from the start of a medicinal product clinical development program, but the burden is mitigated by application of a risk-based approach, with the expectation that the level of effort and documentation in an IMPD should be commensurate with the level of risk, specified by an initial risk analysis based on existing knowledge on the type of product and its intended use. The risk analysis should be updated by the applicant throughout the product life cycle as new data become available. In deciding on the appropriate measures to address the identified risks, the priority should be the safety of subjects enrolled in the trial. The Guideline on strategies to identify and mitigate risks for First-in-Human Clinical Trials with Investigational Medicinal Products (Doc. Ref. EMEA/CHMP/SWP/294648/2007) excludes ATMP, but its principles are nevertheless useful. Aspects to be taken into consideration include the origin of the cells, the type of vector and/or the method used for the genetic modification, the manufacturing process, the non-cellular components and the specific therapeutic use as applicable. The most comprehensive list of ATMP-specific general risk assessment criteria is spelled out in the Human Cell-based Products Guideline.[18]

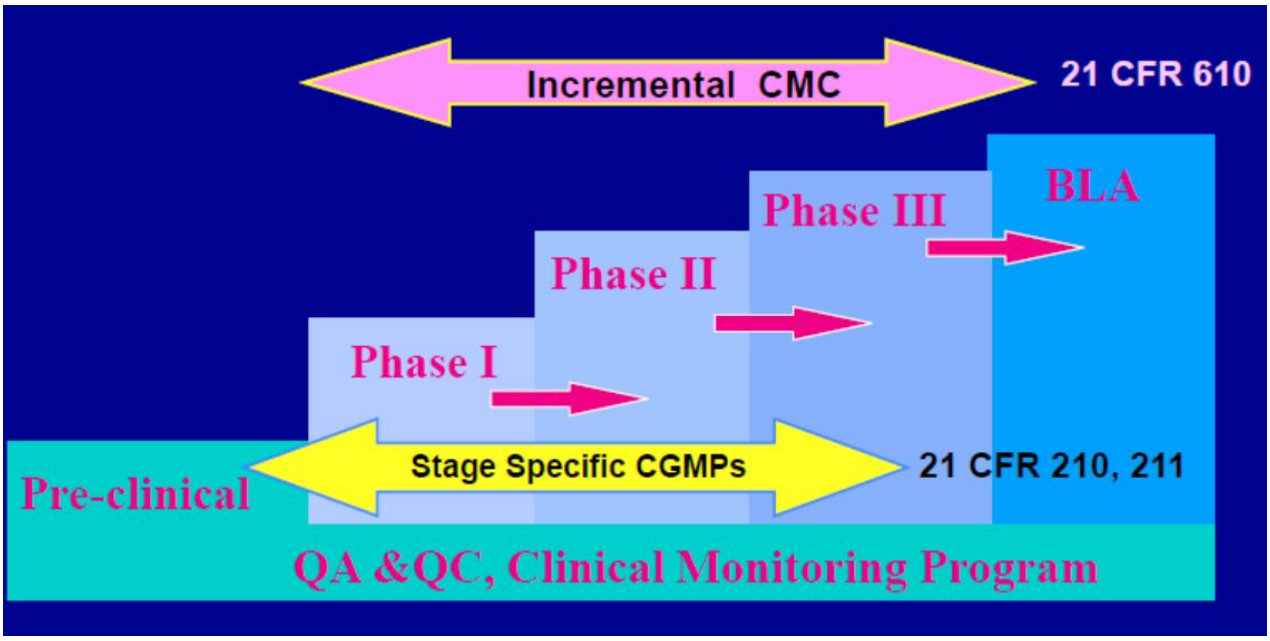
- *origin (autologous-allogeneic)*
- *ability to proliferate and/or differentiate*
- *ability to initiate an immune response (as target or effector)*
- *level of cell manipulation (in vitro/ex vivo expansion/activation/ differentiation /genetic manipulation/ cryo-conservation)*
- *mode of administration (e.g. ex vivo perfusion, local or systemic surgery)*
- *duration of exposure or culture (short to permanent) or life span of cell*
- *combination product (cells and bioactive molecules or structural materials)*
- *availability of clinical data on or experience with similar products.*

[18] Guideline on Human Cell-based Medicinal Products. Doc. Ref. EMEA/CHMP/410869/2006
[19] cGMP for Phase 1 Investigational Drugs. July 2008

In contrast, in the US, an incremental CMC approach to stage specific GMP requirements is being applied. Phase 1 clinical studies are exempt from 21 CFR Part 211 compliance.[19]

cGMP principles that should always be applicable to Phase 1 investigational products are: Sterility assurance, quality oversight and facility control, and adequate documentation (traceability).

The manufacture of investigational products under evaluation in Phase 2 and Phase 3 clinical studies becomes then subject to full compliance of cGMP regulations in 21 CFR Part 211. An exception applies to Phase 1 study investigational products, that have been lawfully marketed, or made available in a Phase 2 or Phase 3 clinical study for a different indication. In this case the Phase 1 study must comply with 21 CFR Part 211.



Source: Denise K Gavin, Division of Cellular and Gene Therapies

Impact: HIGH

Stage specific GMP designed to meet the requirements in the US for a Phase 1 trial would not necessarily meet the requirements set in the EU.

In the EU, a Potency Assay with Acceptance Criteria is required for Ph1/FIH trials

In the US, the FDA recommends an incremental, progressive matrix approach to Potency assay development. For a Phase 1 trial some limited quantitative information of biological activity/attributes must be measured to collect results that will inform the development of a potency assay. A potency assay as final product release assay must be qualified with acceptance criteria limits at the start of a Phase 3/pivotal trial, and fully validated before licensure.[20] In contrast, in the EU, to comply with EMA phase appropriate GMP regulations, a potency assay is required to be qualified with acceptance criteria limits in Phase 1/FIH trials and is expected to be fully validated before the start of a Phase 3/pivotal trial.[21,22]

As stated in the EU ATMP draft guideline.[22]

For a FIH trial the absence of quantitative limits for potency / biological activity would have to be justified by the applicant.

In practice this may be handled differently between member states, as there has been the experience of ARM members, that several FIH studies for ATMP have initiated in the EU (specifically in the UK), without a potency assay, or a formal justification for its absence.

Except for the Potency assay requirement, the timing of cGMP Analytics/Process validation implementation aligns in the US and EU, as required for BLA and MAA[21], respectively. However, the 2019 ATMP draft guideline contains wording that is suggestive of earlier (pivotal trial) validation implementation regulatory requirement.[22]

Impact: HIGH

A FIH study designed to meet the specifications in the US, without quantitative limits for a potency assay, would often not meet the requirements set in the EU.

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[20] Potency Tests for Cellular and Gene Therapy Products. January 2011
[21] EudraLex, The Rules Governing Medicinal Products in the European Union: Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products. Adoption by the European Commission 22 November 2017
[22] Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells. Doc. Ref. EMA/CAT/GTWP/671639/2008 Rev. 1 (26 July 2018)

In the EU, a Qualified Person must ensure GMP compliance and authorizes FP release

In the EU, each manufacturing site must have a Qualified person (QP) to release investigational product or an authorized product, including product that has been imported from outside the EU. QPs responsible for ATMP should have training and experience relevant to the specific characteristics of these products. The QP makes a declaration of compliance with GMP, compliance with the registered dossier, approved procedures and has to audit the manufacturing facility.[21]

As stated in the EU ATMP guideline.[21]

In case of imports of investigational ATMPs from third countries, the QP should ensure that the quality of the batch is in accordance with the terms of the clinical trial authorisation and that it has been manufactured in accordance with quality standards at least equivalent to the GMP requirements applied in the EU

The EU applies a risk-based approach to manufacturing facility inspections, but inspection at the time of license application is common practice.

In the EU, the FDA conducts biannual inspections for approved products, CBER determines, whether Pre-License-Inspections, or Pre-Approval-Inspections are necessary to be conducted as on-site inspections.[23]

However, in a recent development, in April 2019, the FDA finalized revising the biannual biologic facility inspection requirement in 21CFR 600.21 to a risk-based schedule. Resources saved by performing less frequent inspections at lower risk facilities, will allow FDA to inspect facilities deemed to be higher risk more frequently, as required.

Impact: HIGH

US sponsors of an ATMP manufactured in the US with intend to supply clinical trials in the EU, have to secure the services of a QP, who must be located in the EU. The US sponsor also should expect the possibility of a manufacturing facility inspection at license application.

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[23] Compliance Program Guidance Manual Chapter – 45 Biological Drug Products. Inspection of Biological Drug Products (CBER). October 2010

US Cleanroom Air Classification Standards differ from European Guidelines

In the US, the cleanroom air quality classification system had been historically regulated per Federal Standard 209 (Class 100, Class 1,000, Class 10,000, Class 100,000), and nowadays the International Standards Organisation ISO Standards are being used (ISO 5, ISO 6, ISO 7, ISO 8). The EU cleanroom air quality is regulated per Pharmaceutical Cleanroom Classification for Sterile Medicinal products (Grade A, Grade B, Grade C, Grade D).

Grades A and B only approximately correspond with class 100, ISO 5; Grade C with class 10,000, ISO 7 and Grade D with class 100,000, ISO 8. With respect to air quality requirements for open process manufacturing steps that are often employed for ATMP it is stated:

EU ATMP guideline.[21]

Production in an open system: In general, when the product is exposed to the environment (e.g. working under laminar air flow), a critical clean area of grade A with a background clean area of grade B is required for aseptic preparation.

FDA cGMP guideline.[19]

Conducting aseptic manipulation in an aseptic workstation (e.g., laminar air flow workbench, biosafety cabinets, or barrier isolator system) under laminar airflow conditions that meet Class A, ISO 5.

Many US based academic GMP facilities and commercial CDMO cleanrooms will not be compliant to open-process manufacture ATMP for the EU (Requirement Grade A BSC in Grade B background cleanroom), because they have been built to house Class100/Grade A/ISO5 biosafety cabinets in a Class 10,000/ISO 7 background, which has an approximately 10x higher at-rest, non-viable particle limit, compared to the EU Grade B background.

Impact: HIGH

Sponsors planning to open process manufacture ATMP for clinical trials in the EU may encounter a bottleneck of few available EU compliant CDMO cleanroom facilities.

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[19] cGMP for Phase 1 Investigational Drugs. July 2008

In the EU, the QP must oversee that imported drug products are re-tested for batch certification

In the EU, drug products that are imported must be re-tested for release and batch certification by the QP.[21] For ATMP this will often be impractical or not possible. Exemptions can be granted for ATMP if proper justification is provided:

For ATMP it may be justified to rely on testing performed in the third country in cases where the limited amount of material available (e.g. autologous products) or the short shelf-life impedes double release testing. In such cases, the testing in the third country should be conducted in GMP-certified facilities.

As stated in EU ATMP guideline.[21]

When the QP wishes to rely on testing of samples taken in a third country, transport and storage conditions should be adequate, so as to ensure the samples taken in the third country are still representative of the batch

Impact: MEDIUM

While the re-testing requirement for import of US manufactured drug products will be impractical for many ATMP, mechanisms to justify and allow exemptions are in place. These will require a stringent validation of transport and storage conditions for the US manufactured drug product.

[21] EudraLex, The Rules Governing Medicinal Products in the European Union: Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products. Adoption by the European Commission 22 November 2017

Instruments, container closure systems and delivery devices are regulated under the medical device pathways which differ regionally

In the EU, the CE mark ensures that medical devices meet safety, health and environmental protection requirements. However, if automated manufacturing equipment does not qualify as a medical device (not certified for an intended use), the CE mark may not be relevant and does not suffice to demonstrate suitability under ATMP guidelines.[21]

In contrast, the US approach assesses the device's effectiveness as well as its risk of causing harm. Sponsors are faced with a variety of pathways to market approval. Manufacturing equipment that does not meet the definition of a medical device and is evaluated within the context of the biological product IND/BLA. Medical devices are classified in one of three classes based on the risk level posed by the device:

Most Class I and a few Class II-510(k) exempt devices do not require premarket clearance or approval prior to entering the market.

Class II medical devices require a Premarket Notification (510(k)), which involves demonstrating substantial equivalence to a legally marketed 510(k)/Class II device.

Class III medical devices require a Premarket Approval (PMA), which involves demonstrating the safety and effectiveness of the medical device. All novel medical devices are automatically classified as Class III unless a De Novo is granted.

Impact: MEDIUM

An EU-issued CE mark does not qualify for the use as medical device in the US.

[21] EudraLex, The Rules Governing Medicinal Products in the European Union: Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products. Adoption by the European Commission 22 November 2017

In the US, GM-cell therapy FP must be tested for RCR, whereas in the EU RCR testing of the vector starting material may suffice

In the US, a gene-modified cell therapy must undergo release testing for absence of replication-competent virus,[24] but testing requirements can be reduced or waived overtime with accumulation of safety data:

Viral Producer Cell MCB has to be tested in addition to vector supernatant by in vitro assay with cell line that is permissive for RCR infection

The final product of a transduced GM cell therapy has always to be tested for RCR, even if cultured for less than four days, PCR assay can be acceptable if short shelf-life prohibits in vitro infection assay

Consistent manufacturing and clinical evidence that the GM-CT FP is consistently RCR negative, can obtain permission to have testing requirement waived or reduced. If not RCR tested at FP batch release, archive sample for future testing at least 6 months after product expiration date

In contrast, in the EU, the drug substance and appropriate intermediates of replication deficient viral vectors, as well as packaging/producer cell lines should be screened for replication competent viruses (RCV), which may suffice for gene-modified cell therapies

As stated in the EU ATMP draft guideline.[22]

In the case of genetically-modified cells, RCV testing at the Drug Substance or other intermediate levels is not deemed necessary provided that absence of RCVs has been demonstrated at the level of the virus starting material

Impact: LOW

The additional RCV testing of EU sponsor GM-cell therapies for clinical trials in the US, would not be a major cost and time factor, and the requirement can be reduced/waived later on.

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[24] Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up. July 2018
[22] Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells. Doc. Ref. EMA/CAT/GTWP/671639/2008 Rev. 1 (26 July 2018)

In the EU, living cells, even if their function is mostly structural/mechanical, cannot be classified as devices

In the US, human tissue products that contain living cells had been classified as devices, if their function/mechanism of action was mostly structural, e.g. the skin replacement Apligraf received market approval as a Class III medical device subject to Premarket Approval (PMA) regulation.

In contrast, in the EU, products containing living cells cannot be classified as medical devices, independent of their mostly structural vs. metabolic function, e.g. Epithelia, and would be regulated as ATMP

Impact: LOW

It seems less likely that a human product containing living cells would be regulated under PMA in the US today.

LONG-TERM FOLLOW-UP WORKSTREAM

Cell and Gene Therapies are associated with new risks to patients related to the quality, safety and efficacy of the therapies. In the US, these risks are identified throughout the review of the clinical trial Investigational New Drug Applications and the Biologic License Application (BLA) and are addressed through LTFU studies, Post-marketing requirements and commitments as well as Risk Evaluation and Mitigation Strategies (REMS).

Table 5: List of the most important regulatory references related to LTFU study requirements in the US. A full list of references that informed the analysis is found at the end of the report.

Key References for the US	
FDA Draft Guidance for Industry: Long-Term Follow-up After Administration of Human Gene Therapy Products, July 2018	Recommendations regarding the design of LTFU observational studies for the collection of data on delayed adverse events following administration of a GT product
FDA Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products, June 2017	Contains recommendations regarding follow up observations for cell and gene therapy products

In the EU, the risks associated with Advanced Therapy Medicine Products (ATMPs) are addressed through the development of an ATMP Risk Management Plan, which may include LTFU observations, post-marketing safety studies and other pharmacovigilance measures, as well as risk minimization measures including educational programs.

Table 6: List of the most important regulatory references related to LTFU study requirements in the EU. A full list of references that informed the analysis is found at the end of the report.

Key References for the EU	
Discussion paper: Use of patient disease registries for regulatory purposes – methodological and operational considerations, The Cross-Committee Task Force on Patient Registries 5 November 2018, EMA/763513/2018	Discusses methodological and operational aspects of the use of patient disease registries and registry studies for regulatory purposes
Guideline on Safety and Efficacy Follow-Up - Risk Management of Advanced Therapy Medicinal Products, 25 January 2018, EMEA/149995/2008 rev.1	Provides guidance for the Safety and Efficacy follow-up and risk management for advanced therapy medicinal products (ATMPs) according to Article 14(4) of Regulation (EC) No 1394/2007

Guideline on Follow-Up of Patients Administered with Gene Therapy Medicinal Products Doc. Ref. EMEA/CHMP/GTWP/60436/2007	Recommendations for clinical monitoring and follow-up after treatment with Gene Therapy (GT) medicinal products
Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced therapy medicinal products	How to identify the risks associated with the clinical use of an ATMP and their risk factors with respect to quality, safety and efficacy

Summary of Differences Between the US and the EU LTFU Requirements

Following review of the regulatory references listed in Tables 5 and 6, five key differences were identified between the US and EU requirements:

Factor	Impact
1. There are regional differences in vector-specific LTFU study duration recommendations	HIGH
2. US LTFU studies are focused on safety and presence of the vector; EU LTFU studies are focused on safety and efficacy	HIGH
3. In the EU, a 30-year traceability requirement applies to all ATMPs including gene therapies	MEDIUM
4. The EMA promotes the use of patient disease registries based on their initiative for patient registries	MEDIUM
5. Interventional vs. non-interventional study categorization in the EU	MEDIUM

Impact Rating Scale

HIGH: significant different that could result in a LTFU study that is designed to meet the requirements for one region failing to meet the requirements of the other region.

MEDIUM: carries other significant implications for the time and cost associated with the development of the therapy across the US and EU.

LOW: unlikely to cause significant time delays or increase the cost of development.

Differences in vector-specific LTFU study duration guidelines

Both the FDA and the EMA consider that the length of follow-up study required varies depending on the risk profile of the gene therapy vector or gene editing technology, and both agencies have issued guidelines that are product or vector-specific. A comparison of these guidelines reveals differences in the LTFU study duration recommended for plasmids, poxvirus, herpesvirus, adeno virus and AAV vectors (Table 7).

Table 7: Summary of Differences Between the US and EU Vector-Specific LTFU Study Duration Guidelines

Product/Vector Type	Propensity to modify genome?	FDA - LTFU study required?	EMA - LTFU study required?
Plasmid	No	No	Monitoring plan for a total of 5 years. If any post-treatment samples are positive or clinical evaluation indicates a treatment induced adverse reaction, then a more regular and extensive clinical follow-up should be undertaken.
Microbial vectors for gene therapy	No, but may persist and undergo reactivation	Product specific	Product specific
Poxvirus	No	No	Monitoring plan for a minimum of 5 years. If any post-treatment samples are positive or clinical evaluation indicate a treatment induced side effect/adverse event, then a more regular and extensive clinical follow-up should be undertaken.
Adenovirus	No	No	
Adeno-associated virus (AAV)	No, but capable of long-term expression without integration	Product-specific (2-5 years)	

Herpesvirus	No, but may undergo latency/reactivation	Yes - Clinical protocols should include LTFU observations with a duration of 15 years. A risk-based approach for determining the duration of a LTFU protocol may be considered for vectors capable of latency (e.g. Herpesvirus).	Yes - It is usually expected to follow the patients up to 15 years. Monitoring plan time points: pre-treatment, 3, 6 and 12 months after treatment for at least 5 years, and then yearly until data indicate that there is no longer any risk to be followed.
Gammare-trovirus	Yes		
Lentivirus	Yes		
Transposon elements	Yes	Product specific	No specific guideline
Genome editing products	Yes; permanent changes to the host genome	Yes - 15 years	No specific guideline
Genetically modified cells		Follow recommendations for the gene therapy vector used	Follow the recommendations for the gene vector used unless non-clinical or clinical data indicate a need for a different follow-up regimen

Impact: HIGH

A LTFU study designed to meet the specifications in one region would not necessarily meet the requirements set in the other region.

US LTFU studies are focused on safety and persistence of the vector; EU LTFU studies are focused on safety, efficacy and vector persistence

In the US, LTFU observations are required to address safety issues and vector persistence only, with certain exceptions (e.g. pediatric study requirements). Efficacy measures can be included on a voluntary basis.

In contrast, in the EU, ATMP Risk Management Plans encompass both safety and efficacy assessments, as loss of expected efficacy over time is considered to be a risk that must be addressed.[25]

Impact: HIGH

A LTFU study designed to meet the specifications in the US would not necessarily meet the requirements set in the EU.

[25] Guideline on Safety and Efficacy Follow-Up - Risk Management of Advanced Therapy Medicinal Products, 25 January 2018, EMEA/149995/2008 rev.1

In the EU, a 30-year traceability requirement applies to all ATMPs including gene therapies

As stated in the EU Guideline:

> *"The marketing authorisation holder or sponsor of a clinical trial with a Gene Therapy product shall ensure that traceability data on the sourcing, manufacturing, packaging, storing, transport and delivery to the hospital, institution or private practice where the product is used, are in accordance with Regulation (EC) No 1394/2007 (art. 15) This regulation establishes the requirement to maintain traceability records for 30 years."*[26]

In the US, gene therapy license holders and sponsors are not required to meet such long term traceability requirements.

Impact: MEDIUM

Gene therapy facilities must establish and maintain policies and procedures that allow for an extended record retention period in the EU.

[26] Guideline on Follow-Up of Patients Administered with Gene Therapy Medicinal Products Doc. Ref. EMEA/CHMP/GTWP/60436/2007

Use of patient disease registries is promoted in the EU

EMA's initiative for patient registries, launched in September 2015, is focused on expanding the use of patient registries by introducing and supporting a systematic and standardized approach to their use for regulatory purposes. As part of this effort, EMA has set up a cross-committee task force on registries and has created an inventory of patient registries in the resources database of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). The inventory aims to facilitate the interaction between stakeholders and existing patient registries. EMA also conducted disease-specific workshops where participants provided recommendations on the use of registries in several disease areas, including input on core data elements, consent documents, governance, data sharing and interoperability. The EMA cross-committee task force published a discussion paper on methodological and operational considerations in the use of patient disease registries for regulatory purposes in November 2018.[27]

By contrast, the US FDA has not released guidance on this topic.

Impact: MEDIUM

Both the EMA and FDA have established a track record of accepting the use of patient disease registries for LTFU studies for cell therapy products.

[27] Discussion paper: Use of patient disease registries for regulatory purposes – methodological and operational considerations, The Cross-Committee Task Force on Patient Registries 5 November 2018, EMA/763513/2018

Interventional vs. non-interventional study categorization in EU

In the EU, LTFU observations may be categorized as interventional or non-interventional studies depending on the study design and the relevant national authority. In general, a patient registry is typically classified as non-interventional and would therefore fall outside of the scope of the EU CT Directive (2001/20/EC). Most registries only need ethics committee approval in most EU member states with some countries requiring only a notification to the regulatory authority but not review and approval. However, in some cases, a patient registry study (or LTFU study) could be considered as interventional, depending on the protocol, and would therefore be within the scope of the CT Directive and would need to have both regulatory authority and ethics committee approval to allow it to begin.

The category assigned to the LTFU study (interventional or not) can differ among EU member states. There are additional complexities associated with Direct-to-Patient follow up studies (such as a study that involves having patients fill out a PRO each year during the LTFU period) and how they are categorized across different EU member states.

Differences in how a single study is categorized across EU member states will be addressed by the implementation of the new Clinical Trials Regulation, which will create a single authorization procedure for all clinical trials. However, there may continue to be issues with respect to consistency in interventional vs. non-interventional study categorization from one study to the next.

Impact: MEDIUM

Unexpected differences in study categorization, and the associated regulatory requirements that must be met prior to initiation of the trial, can cause significant delays in clinical trial start up.

APPENDIX A

EU Competent Authorities for Tissues and Cells

Member States	Competent Authorities	Website of the Competent Authorities
Austria	Austrian Federal Office for Safety in Health Care	https://www.basg.gv.at/en/home/
Belgium	Federal Agency for Medicines and Health Products	https://www.famhp.be/en.
Bulgaria	Bulgarian Executive Agency for Transplantation	http://www.bgtransplant.bg/iat/index.php
Croatia	Ministry of Health	https://zdravstvo.gov.hr/
Cyprus	Ministry of Health	https://www.moh.gov.cy/moh/moh.nsf/index_en/index_en?OpenDocument
Czech Republic	Ministry of Health State Institute for Drug Control	https://www.mzcr.cz/en https://www.sukl.cz/en
Denmark	Danish Patient Safety Authority	https://stps.dk/en
Estonia	State Agency of Medicines	http://www.ravimiamet.ee/
Finland	Finnish Medicines Agency (Fimea)	http://www.fimea.fi/web/en
France	Ministry of Health Agence nationale de sécurité du médicament et des produits de santé (ANSM) Agence de la Biomédecine	http://solidarites-sante.gouv.fr/ http://ansm.sante.fr/ https://www.agence-biomedecine.fr/
Germany	German Federal Ministry of Health Paul-Ehrlich-Institut	https://www.bundesgesundheitsministerium.de/en/?L=1 https://www.pei.de/EN/home/node.html
Greece	Ministry of Health Hellenic Transplant Organisation and Bone Marrow Department Hellenic National Authority for Medically Assisted Reproduction – Ministry of Health	http://www.moh.gov.gr/ http://www.eom.gr/ www.eaiya.gov.gr
Hungary	Ministry of Human Capacities	http://www.kormany.hu/en/ministry-of-human-resources

Ireland	Health Products Regulatory Authority	https://www.hpra.ie/
Italy	Ministry of Health National Blood Centre Centro Nazionale Trapianti (CNT)	http://www.salute.gov.it/portale/home.html http://www.centronazionalesangue.it/ http://www.trapianti.salute.gov.it/cnt/cnt.htm
Latvia	State Agency of Medicines	https://www.zva.gov.lv/
Lithuania	Ministry of Health National Transplants Bureau – Ministry of Health State Health Care Accreditation Agency – Ministry of Health	http://sam.lrv.lt/ http://ntb.lrv.lt/ http://www.vaspvt.gov.lt/en
Luxembourg	Ministry of Health	http://www.sante.public.lu/fr/index.php
Malta	Ministry of Health - Superintendence of Public Health	https://deputyprimeminister.gov.mt/en/sph/Pages/Superintendence-of-Public-Health.aspx
Poland	National Centre for Tissues and Cells Banking Polish Transplant Coordination Centre – Poltransplant Department of Mother and Child – Ministry of Health	http://www.kcbtik.pl/ http://www.poltransplant.org.pl/ https://www.gov.pl/zdrowie/
Portugal	Instituto Português do Sangue e da Transplantação Direção-Geral da Saúde (DGS) Conselho Nacional de Procriação Medicamente Assistida	http://ipst.pt/ https://www.dgs.pt/ http://www.cnpma.org.pt/
Romania	National Transplant Agency Ministry of Health	https://www.transplant.ro/ http://www.ms.ro/
Slovakia	Ministry of Health	http://www.health.gov.sk/Index.aspx
Slovenia	Agency for Medicinal products and Medical Devices of the Republic of Slovenia Slovenija-transplant	http://www.jazmp.si/ http://www.slovenija-transplant.si/
Spain	Organización Nacional de Trasplantes (ONT) National Commission on ARTs	http://www.ont.es/Paginas/Home.aspx http://www.cnrha.msssi.gob.es/

Sweden	Health and Social Care Inspectorate Medical Products Agency National Board of Health and Welfare	https://www.ivo.se/ https://lakemedelsverket.se/ http://www.socialstyrelsen.se/
The Netherlands	Ministry of Health, Welfare and Sport Health and Youth Care Inspectorate	https://www.government.nl/ministries/ministry-of-health-welfare-and-sport https://www.igj.nl/
United Kingdom	Human Fertilisation and Embryology Authority Human Tissue Authority	https://www.hfea.gov.uk/ www.hta.gov.uk

APPENDIX B: LABORATORIES LOCATED OUTSIDE OF THE US THAT ARE CLIA-CERTIFIED

Source: CMS website

https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/CLIA_Laboratory_Demographic_Information.html

Search performed using state = “FN”

Certificate / Application Type	Name and Address / CLIA Number	Telephone #	Certificate Expiration Date	Lab Testing Performed In
Accreditation	**3dmed Inc Clinical Laboratory** Kangxin Road Pudong New Area 8f, #25 Lane 3399 Shanghai 200120 China , Fn #99d2166030	(212) 090-9800	5/21/2021	Independent
Accreditation	**Advanced Genomic Solutions (Ags) Ltd** 16/F Chuang's Tower, 30-32 Connaught Road Central Hong Kong Hong Kong , Fn #99d2143058	(852) -26-1829	4/23/2020	Independent
Accreditation	**Agendia Nv** Science Park 406 Matrix V, 3rd Floor Amsterdam 1098xh The Netherlands , Fn	( ) -	4/3/2021	Other

	#99d1030869			
Accreditation	**Almac Diagnostics** 19 Seagoe Industrial Estate Craigavon Bt63 5qd United Kingdom , Fn #99d2017022	(283) 833-7575	10/30/2019	Independent
Compliance	**Asper Biogene Llc** Vaksali 17a Tartu 50410 Estonia , Fn #99d2046227	(372) 730-7295	12/12/2020	Independent
Accreditation	**Bgi Tech Solutions (Hong Kong) Co Ltd** 16 Dai Fu Street Tai Po Industrial Estate New Territories Hong Kong Hong Kong , Fn #99d2135851	(852) -35-9221	9/7/2019	Independent
Accreditation	**Bioscientia Gmbh** 17 Konrad Adenauer-Str Ingelheim 55218 Germany , Fn #99d0999793	(496) 132-7810	4/30/2020	Independent
Accreditation	**Blueprint Genetics** Biomedicum 1 Haartmaninkatu 8 Helsinki 00290	(850) 527-1295	4/20/2021	Independent

	Finland , Fn #99d2092375			
Compliance	**Burning Rock & Ctong Laboratory** Unit 601 Bldg 3 Industrial Pk Phase 2 Guangzhou Guangdong 510300 China , Fn #99d2123798	(862) 034-0378	1/25/2021	Independent
Accreditation	**Caprion Biosciences Inc** 201 Avenue President Kennedy Suite 3900 Montreal Quebec H2x347 Canada , Fn #99d2126355	((51) 4)3-35-5	8/8/2019	Other
Accreditation	**Cegat Gmbh-Center For Genomics And Transcriptions** Paul-Ehrlich-Strasse 23 Tuebingen 72076 Germany , Fn #99d2130225	(49) 707-1565	6/20/2021	Independent
Accreditation	**Center For Nephrology And Metabolic Disorders** Werner-Seelenbinder-Str 73 Weisswasser D-	(357) 621-5522	3/19/2020	End Stage Renal Disease Facility

	02943 Germany , Fn #99d1063776			
Accreditation	**Centogene Gmbh Rostock** Ag Am Strande 7 Rostock 18055 Germany , Fn #99d2049715	(938) 120-3652	4/2/2021	Independent
Registration	**Centro Consulenza Anatomia Patologica Oncologico** Via Saint Bon 20 Milano 20147 Italy , Fn #99d0971492	(024) 831-7649	11/27/2013	Independent
Compliance	**Cgc Centro De Genetica Clinica** Rua Sa Da Bandeira, 706-1 Porto 4000-432 Portugal/Azores , Fn #99d1066287	(003) 512-2338	8/6/2020	Independent
Accreditation	**Cirion Biopharma Research Inc** 3150 Delaunay Laval Quebec H7l5e1 Canada , Fn #99d2079197	(450) 688-6445	7/8/2020	Other
Accreditation	**Clinical Genomics Centre**	(416) 58-6 48	5/15/2020	Independent

	600 University Avenue, Room 6-423 Toronto, Ontario M5g1x Canada , Fn #99d2144057			
Accreditation	**Contextual Genomics** 204-2389 Health Sciences Mall Vancouver, Bc V6t-1z3 Canada , Fn #99d2111438	(778) 379-2931	3/21/2021	Independent
Accreditation	**Cytogenetics And Molecular Diagnostics** Uhn/Lab Med Prg/200 Elizabeth St, Eaton 11-444 Toronto, Ontario M5g 2c4 Canada , Fn #99d1106115	(416) 340-4800	4/20/2020	Hospital
Accreditation	**Dna Vision Sa** 25 Ave Georges Lemaitre Gosselies B 6041 Belgium , Fn #99d1055506	(327) 137-8527	6/10/2021	Independent
Accreditation	**Dynacare** 115 Midair Court Brampton, Ontario L6t5m3 Canada , Fn #99d0968796	(905) 790-3000	6/13/2021	Other

Accreditation	**Dynacare-Gamma Laboratory Partnership** 245 Pall Mall Street London, Ontario N6a1p4 Canada , Fn #99d0968792	(519) 679-1630	6/13/2021	Independent
Accreditation	**European Laboratory Of Nutrients** Regulierenring 9 La Bunnik 3981 The Netherlands , Fn #99d0990365	( ) -	1/14/2021	Insurance
Accreditation	**Genetrack Biolabs Inc** 200-2806 Kingsway Vancouver, British Columbia V5r 5t5 Canada , Fn #99d1107498	(604) 325-7282	12/29/2019	Independent
Accreditation	**Genetron Health Beijing Co Ltd** 1f Builiding 11 Zone 1,8 Life Science Parkway Chanping District Beijing 10220 China , Fn #99d2141165	(860) 105-0907	1/10/2020	Independent
Compliance	**Haliodx Sas** 163 Avenue De Luminy	(049) 129-3090	6/6/2019	Independent

	Marseille 13009 France , Fn #99d2131292			
Accreditation	**Hangzhou Veritas Genetics Bio Tech Co Ltd** 11th Floor Leo Building No 2 Science And Technology Park Road Hangzhou 31001 Ch , Fn #99d2134541	(86-) 571--282	8/17/2019	Industrial
Compliance	**Health In Code** Edificio O Fortin, Hospital Maritimo De Oza As Xubias S/N A Coruna 15006 Spain , Fn #99d2153048	((48) 8)1-60-0	10/8/2020	Independent
Accreditation	**Histogenex N V** Sint-Bavostraat 78-80 B-2610 Wilrijk B-2610 Belgium , Fn #99d1095931	(323) 280-4860	10/25/2019	Independent
Accreditation	**Icon Central Laboratories - Dublin** South County Business Park - Leopardstown Dublin 18 Ireland , Fn	(631) 306-5577	7/20/2019	Other

	#99d2013537			
Compliance	**Igenomix** Calle Narcis Monturiol Estarriol N'11 Parcela B, Edifico Europark Valencia 46980 Spain , Fn #99d2146167	(349) 639-0531	6/3/2020	Other
Accreditation	**Impact Genetics Inc** Unit #4 1100 Bennett Road Bowmanville, Ontario L1c 3k5 Canada , Fn #99d0990947	(647) 478-4902	10/7/2020	Hospital
Registration	**Inagene Diagnostics Inc** 790 Bay Street Suite 935 Toronto Ontario Canada , Fn #99d2164194	(647) 346-0990	3/28/2021	Independent
Compliance	**Laboratory Of Clinical Pharmacology Unit-** 3175 Ste-Catherine Road Dept Of Biochemistry (Room 2943) Montreal, Quebec , Fn #99d2152806	((51) 4)3-45-4	9/25/2020	Hospital

Accreditation	**Life Length Sl** Calle Faraday 7 First Floor Madrid 28049 Spain , Fn #99d2112462	(349) 173-7129	8/8/2020	Independent
Accreditation	**Macrogen Hq** 254 Beotkkot-Ro Geumcheon-Gu Seoul 08511 South Korea , Fn #99d2158117	((30) 1)2-51-1	1/21/2021	Independent
Accreditation	**Macrogen Pmc** 6f 172 Dolma-Ro Bundang-Gu Seongnam-Si Gyeonggi-Do 13605 South Korea , Fn #99d2158119	((30) 1)2-51-1	1/21/2021	Independent
Registration	**Mcgill University Health Center** E05 5051 1001 Boul Decarie Montreal Qc H4a 3j1 Canada , Fn #99d1042152	(514) 934-1934	5/8/2020	Hospital
Accreditation	**Mlm Medical Labs** Dohrweg 63 Moenchengladbach 41066 Germany , Fn #99d1100191	(49) 21 -61 4	8/25/2019	Independent

Compliance	**Mogen Body Genetics Lab** 6b, Kiryat Mada St. Har Hozvim Jerusalem 91450 Israel , Fn #99d1101256	( ) -	8/10/2019	Other
Accreditation	**Molecular Genetics Division** Department Paediatric Medicine, 555 University Ave Toronto Ontario M5g 1x8 Canada , Fn #99d1014032	(416) 813-6590	8/17/2020	Hospital
Accreditation	**Molecular Health Gmbh** Kurfurstenanlage 21 Heidelberg 69115 Germany , Fn #99d2112168	(496) 221-4385	7/26/2020	Independent
Accreditation	**Mvz Labor Dr Quade Und Kollegen Gmbh** Aachener Strasse 338 Cologne Nrw D50933 Germany , Fn #99d2114965	(492) 219-4056	9/6/2020	Independent
Registration	**Nanjing Shihe Jiyin Biotech Inc.**	(011) 862-5584	10/22/2020	Independent

	3-1 Xinjinhu Rd, Sino-Danish Nanjing Hitech Park, Bld G 2 17th Floor Nanjing Jiangsu 211032 China , Fn #99d2156674			
Compliance	**Neo New Oncology Gmbh** 20, Gottfried- Hagen-Strasse Cologne 51105 Germany , Fn #99d2134325	(004) 9-2-21-8	8/28/2019	Independent
Accreditation	**Nipd Genetics Limited** 31 Neas Engomis St, Engomi Nicosia 2409 Cyprus , Fn #99d2131696	(357) 222- 6688	2/29/2020	Other
Compliance	**Pacific Edge Diagnostics New Zealand** 87 St David Street Level 1 Dunedin New Zealand , Fn #99d2064747	(643) 479- 5800	10/31/2019	Independent
Compliance	**Phenogen Sciences Laboratories** 60-66 Hanover Street	(613) 841- 2700	11/16/2019	Independent

	Fitzroy, Victoria 3065 Australia , Fn #99d2023356			
Registration	**Phsa Laboratories - Ctag** 3rd Fl 600 W 10th Ave Vancouver Bc V5z 4e Canada , Fn #99d2000767	(604) 877-6000	12/3/2015	Other
Compliance	**Raymond L Barnhill Md Consultation Service** 26 Rue D'ulm 75248 Paris Cedex 05 France , Fn #99d2079198	(314) 432-4250	7/16/2020	Independent
Compliance	**Repeat Diagnostics** 309-267 West Esplanade Ave North Vancouver, British Columbia V7m 1a5 Canada , Fn #99d1068060	(604) 675-8000	1/24/2020	Independent
Accreditation	**Riken Genesis Co Ltd** Life Innovation Center, 3-25-22, Tonomachi Kawasakishi, Kanagawa 210-0821 Japan , Fn #99d2094732	( ) -	12/29/2019	Independent

Registration	**Shanghai Origimed Clinical Laboratory** 5th Floor, Building 3 No 115 Xinjunhuan Rd, Minhang District Shanghai 20 , Fn #99d2159871	(860) 213-4780	12/27/2020	Independent
Compliance	**Shriners Hospital For Children Canada** 1003 Boulevard Decarie Room S1 51 Montreal Quebec H4a0a9 Canada , Fn #99d2153709	(514) 282-8329	9/24/2020	Hospital
Compliance	**Sistemas Genomicos, S L** Parque Tecnologico De Valencia Ronda G Marconi Valencia 6-46980 Spain , Fn #99d2077066	(349) 613-6615	5/5/2020	Independent
Accreditation	**Srl Inc** 1006-1 Komiyamachi, Hachioji-Shi Tokyo 192-0031 Japan , Fn #99d2103945	(011) 814-2648	9/26/2019	Independent

Accreditation	**Srl Inc-Hamura Laboratory** 3-5-5 Midorigaoka Hamura-Shi Tokyo 205-0003 Japan , Fn #99d2121802	(81) 42 -579	11/21/2019	Independent
Accreditation	**Targos Molecular Pathology Gmbh** Germaniastrasse 7 Kassel 34119 Germany , Fn #99d2071366	(561) 500-4529	3/9/2020	Independent
Compliance	**Vu University Medical Center** De Boelelaan 1117 1081 Hv Amsterdam, The Netherlands Amsterdam 1081 , Fn #99d1040080	(312) 044-4387	10/17/2017	Hospital
Accreditation	**Wuxi Nextcode Genomics Shanghai Co Limited** 240 Hedan Road Waigaoqiao Free Trade Zone Shanghai 200131 China , Fn #99d2064856	(862) 150-4641	1/19/2020	Independent

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50. Issues identified by stakeholders: follow-up from EMA's ATMP workshop February 2017

51. EMA Report on CAR T-cell therapy Registries Workshop 9 February 2018, report published 15 May 2018

52. CAR T-cell therapy Registries Workshop Appendix 1: Proposed data elements relating to Efficacy and to Safety 18 May 2018

53. EMA CHMP GUIDELINE ON SAFETY AND EFFICACY FOLLOW-UP - RISK MANAGEMENT OF ADVANCED THERAPY MEDICINAL PRODUCTS December 2008

54. EMA CHMP GUIDELINE ON FOLLOW-UP OF PATIENTS ADMINISTERED WITH GENE THERAPY MEDICINAL PRODUCTS 1 May 2010

55. EMA CAT Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced therapy medicinal products 11 February 2013

56. EMA CHMP QUESTIONS AND ANSWERS ON GENE THERAPY December 2009

57. EMA Reflection paper on management of clinical risks deriving from insertional mutagenesis April 2013

58. EMA Report on Haemophilia Registries Workshop 8 June 2018, published 28 September 2018

59. EMA The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (Revision 7)

60. REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

US

61. Rare Diseases: Common Issues in Drug Development FDA Guidance for Industry DRAFT GUIDANCE revision 1 February 2019

62. Long Term Follow-Up After Administration of Human Gene Therapy Products FDA Draft Guidance for Industry July 2018

63. FRAMEWORK FOR FDA'S REAL¬ WORLD EVIDENCE PROGRAM December 2018

64. Statement from FDA Commissioner Scott Gottlieb, M.D., on FDA's new strategic framework to advance use of real-world evidence to support development of drugs and biologics December 2018

65. FDA Guidance for Industry Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events November 2006

66. Use of Electronic Health Record Data in Clinical Investigations FDA Guidance for Industry July 2018

ARM Comments

67. FDA RWE ARM Comments Final (Re: Docket No. FDA-2018-N-4000 "Framework for a Real-World Evidence Program; Availability")

68. ARM Response to EBMT Registry August 2018

BIOGRAPHIES

Project Lead and Expert in Donor Eligibility Policy: Dr. Caitilin Hamill, PhD MBA – Senior Director, Regulatory Affairs, IQVIA's Cell and Gene Therapy Center

Dr. Caitilin Hamill is the head of regulatory affairs for IQVIA's Cell and Gene Therapy Center, where she advises companies on integrated planning, regulatory, and clinical development strategy. Prior to joining IQVIA, Caitilin spent seven years at the US Food and Drug Administration (FDA).

Caitilin served as a reviewer in the Center for Biologics Evaluation and Research (CBER) Office of Tissues and Advanced Therapies (OTAT, formerly OCTGT) where she reviewed Investigational New Drug (IND) applications for cell therapies and Pre-Market Notifications [510(k)s] for devices used in the collection, processing, testing and administration of cell and tissue-based therapies. Caitilin also evaluated performance data for Biologic License Applications for in vitro diagnostic devices used for donor screening and recommended action. Caitilin played an active role in cell and gene therapy policy initiatives contributing to the development of more than 30 guidance documents and regulations including guidance related to donor eligibility determinations. She represented the office on the FDA Personalized Medicine Cross-Center Team and recommended policies for regulation of in vitro diagnostics used to match donors to recipients of cellular therapies.

After three years, Caitilin was promoted to a position in CBER's Office of the Director where she was responsible for Center-level management of CBER's review programs. She identified and assessed emerging complex issues, often resulting from implementation of new legislation, and formulated appropriate programmatic review actions. Caitilin served as a point person and oversaw systems for consistent review and dissemination of review policy, both within and outside of CBER/FDA. This included coordination, development and implementation of CBER review policy and practice with CDER, CDRH, Commissioner's Office, other FDA components and other agencies, where necessary. Caitilin represented FDA on three international committees and negotiated agreements that met FDA's requirements.

Caitilin continues to pursue her passion for cell and gene therapy policy initiatives as an active member of ARM's regulatory committee.

Caitilin earned her Ph.D. in Neuroscience from Northwestern University and received her postdoctoral education in human embryonic stem cell biology under Prof. Matthias Hebrok at the University California San Francisco. Caitilin earned an MBA in finance from The Wharton School, University of Pennsylvania.

GMP Requirements Lead: Dr. Thorsten Gorba, PhD, Translating Center Director of IQVIA's Cell and Gene Therapy Center

Dr. Thorsten Gorba is the principal source of cell and gene therapy CMC expertise at IQVIA. Dr. Gorba brings to this role extensive experience in stem cell research and clinical stage translation,

having worked in and with leading academic groups and industry, and in alliance partnerships, including European Framework, large-scale Research Consortia. As Translating Center Director, Thorsten provides consultative support to inform development of cGMP-compatible manufacturing processes to IND-enabling projects and to manufacture cell therapies under cGMP for use in preclinical and clinical studies. Thorsten also supports technology transfer to external manufacturing organizations and assists with the necessary regulatory filing support.

Previously he has held management level positions in the Regenerative Medicine biotechnology sector at Living Cell Technologies Ltd., Stem Cell Sciences Ltd. and StemCells Inc., involved in all aspects of the regenerative medicine field; translational and preclinical research, stem cell-based screening of small molecules and protein factors, CMC assay and process development, culture automation, GMP manufacturing and regulatory filings. Successful stem cell assay/screening projects for Pharmaceutical industry clients included Sanofi and Pfizer. Dr. Gorba earned his Ph.D. in Developmental Neuroscience from Ruhr-University Bochum, Germany and received his postdoctoral education in Stem Cell Biology under Prof. Austin Smith at the University of Edinburgh, UK.

Thorsten is an active member of ARM's Science and Technology Committee and contributed to the inaugural 2017 and 2018 ARM CMC Workshops, primarily during the comparability & standards breakout sessions. Thorsten also plans to volunteer to the 'A-Cell' development and manufacturing of cell therapies case study booklet project, initiated for 2019 by the S&T Committee.

Senior Advisor on EU Policy, Long-Term Follow-Up Studies and the Use of Registries for Real World Evidence Generation:

Dr. Stella Blackburn is currently Vice President, Global Head of Early Access & Risk Management, Real World Evidence Solutions at IQVIA. She joined IQVIA in April 2014 after spending more than 25 years working in pharmacovigilance and pharmacoepidemiology in regulatory and pharmaceutical industry environments.

Following medical training at Cambridge University and Guy's hospital, Stella worked in hospital medicine before joining the pharmaceutical industry. There, she spent 11 years working in pharmacovigilance and pharmacoepidemiology, gaining an MSc in Epidemiology from the London School of Hygiene and Tropical Medicine. In 1997 she joined the European Medicines Agency (EMA) where she stayed for almost 17 years in a variety of pharmacovigilance and pharmacoepidemiology posts. For the last 10 years at the EMA, Stella was responsible for developing EU policy on risk management, writing the EU guidelines on this topic and more recently as part of the core team helping to implement the 2010 PhV legislation. She was part of the original steering group developing the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and was the Alternate Coordinator, and a scientific work package leader, of IMI PROTECT.

Stella is a Fellow of the International Society of Pharmacoepidemiology (ISPE), the Royal College of Physicians of Edinburgh and the Faculty of Pharmaceutical Medicine. She is a past President of ISPE – the first full-time regulator to hold this post - an honorary lecturer at the London School of Hygiene and Tropical Medicine and Visiting Scientist at Massachusetts Institute of Technology (MIT).

Advisors on EU Guidelines and Multinational Cell and Gene Therapy Development

Dr. Trevor Walker DPhil, MTOPRA – Director, Regulatory Affairs, IQVIA, UK

Trevor gained his doctorate (DPhil) from the Department of Pharmacology, University of Oxford in 1993, and this was followed by 13 years of post-doctoral academic research in various areas of human disease. He then took on a role as a GMP Scientist for 2 years with a small manufacturing company who specialized in the manufacture of stem cell-based therapies before transitioning into regulatory affairs when he joined IQVIA and was involved in a range of global clinical trials, and including involvement with ATMPs. Trevor then moved to PRA Health Sciences where he gained further experience in global clinical trials, and part of his role was as an SME providing regulatory support for ATMP clinical trials. More recently, he has spent three years with Medpace in their Regulatory Affairs group where he was involved in developing ATMP regulatory expertise within the company, scientific advice procedures (EU NCA and EMA), pre-IND and IND activities with the FDA, and provided strategic support and input for ATMP clinical trials. He was also the company's regulatory SME for ATMPs.

Gabriel Bohl MTOPRA – Associate Director, Regulatory Affairs, IQVIA, France

Gabriel has recognized regulatory expertise in supporting large clinical studies, with innovative ATMP/GMO vaccines. He has also expertise in writing/reviewing IMPDs, and in advising companies with regulatory oversight.

He is currently leading the ATMP/GMO SME expert group of the Regulatory Advisor team within IQVIA since 2015 and has been a TOPRA in France Lead since 2014.

He joined the IQVIA European Regulatory Affairs group based in France in 2004 providing support to customers with the assessment of pharmaceutical part of registration dossiers and IMPDs, regulatory advice, and regulatory input for multinational clinical trials as well as experience with Late Phase and non-interventional trials. Previously he spent 2 years at the European Pharmacopeia as a pharmaceutical assessor and worked for 7 years in the pharmaceutical industry in project management and international regulatory affairs.