european biopharmaceutical enterprises

EBE Position Paper:

Tissue and Cells for the Manufacture of Allogeneic Medicinal Products for multiple patients and/or indications:

Need for Convergence of Donor Testing Requirements prior to Procurement of Tissue and Cells

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Executive Summary

In order to protect patients from potential transmissible diseases in allogeneic tissue and cell-based products, there is a need to have a systematic approach to reduce risks by selecting donors and testing for known pathogens. This is done using test methods that are sensitive and validated for intended use and in a testing facility that has Quality Systems and is approved by the Health Authority. However, currently there is no harmonised approach for donor eligibility and testing in the European Union (EU), as well as between the EU and the United States of America (USA) or Japan. This means that that Sponsors developing tissue and cell based products, for the treatment of multiple patients where the same tissue/cell source material is used, internationally, need to reconcile multiple regulations where they currently exist and anticipate requirements in emerging markets. This may limit the availability of transformational products to patients.

This Position Paper sets out the challenges, and recommends clarification and convergence of donor testing requirements, development of more sensitive test methods and of international standards.

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1. Introduction

This position paper deals with the lack of harmonization concerning donor testing requirements across the Member States of the European Union (EU), between the EU and the USA, and between the EU and Japan, as pertinent to the global development of allogeneic fresh and frozen tissue and cell based products for the treatment of multiple patients using the same tissue/cell source material, which is often banked prior to the manufacture of these products.

In order to protect patients from potential transmissible diseases in allogeneic tissue and cell based products there is a need to have a systematic approach to reduce risks by selecting donors and testing for known pathogens using test methods that are sensitive and validated for intended use and in a testing facility that has Quality Systems and is approved by the Health Authority. However, currently there is not a harmonized approach for donor eligibility and testing in the EU. This means that that Sponsors developing tissue and cell based products, for the treatment of multiple patients where the same tissue/cell source material is used, internationally, need to reconcile multiple regulations where they currently exist and anticipate requirements in emerging markets. This may limit the availability of transformational products to patients. Even in the EU there are differences between Member States.

2. Challenges of allogeneic living donor testing for the global development of allogeneic tissue and cell based medicinal products, where multiple patients are treated using the same tissue/cell source from a European perspective

According to Directive 2009/120/EC, amending Directive 2001/83/EC of the European Parliament and of the Council on the Community Code relating to medicinal products for human use as regards advanced therapy medicinal products (ATMPs), donation, procurement, and testing of the human tissue and cells used as starting materials for the manufacture of somatic cell therapy medicinal products (SCTPs), tissue engineered products (TEPs), and genetically modified cell based products (i.e. gene therapy medicinal products (GTs)), should be performed in accordance with Directive 2004/23/EC[1], as amended (Directive 2006/17/EC[2] and Directive 2006/86/EC[3]; European Cells and Tissue Directives (EUCTD) or in accordance with the Blood Directive 2002/98/EC[4], depending on the source of the cells). As laid out in Directive 2006/17/EC, implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells, the use of tissues and cells for application in the human body carries a risk of disease transmission and other potential adverse effects in recipients. That risk can be reduced by careful donor selection, testing of each donation, and the application of relevant procedures.

The donor testing requirements for the USA are described in 21 CFR Parts 210, 211, 820, and 1271 (eligibility determination for donors of HCT/Ps) and additional guidances[5]. The corresponding requirements in Japan are described in PFSB/MHLW Notification No. 1314 (12/12/2000)[6], Notification No. 0907-03 (07/09/2012)[6], and Notification No. 1002/27: Partial Revision of the Standards for Biological Ingredients (MHLW Notification (KOKUJI) No. 375/2014 (02/10/2014)[6].

The key elements where there is currently a lack of harmonization are indicated below:

1) The competent authority or authorities shall ensure that: a) donors of tissues and cells, except donors of reproductive cells, undergo the biological tests set out in point 1 of Annex II of the Directive 2006/17/EC; b) the tests referred to in point (a) are carried out in compliance with the general requirements set out in point 2 of this Annex II. Extensive donor screening and testing may contribute to high safety standards for cells and tissues and therefore to the protection of

human health, which includes health of patients, health care providers, operators, handling of the tissues and cells at the tissue establishment and in the manufacturing plant, and other people coming into contact with the tissues and cells. As specific donor tests cannot (always) be repeated using retained samples of the donor blood/tissue, it is critical to be aware of national testing requirements and apply all these at the time of donor testing. However, this is often not feasible, as the donation of the tissue/cell and donor eligibility assessment occurs prior to or concurrently with the procurement of the tissues and cells by a Sponsor for the manufacture of tissue and cell based products. It may also be the case that at the time of tissue/cell procurement it may not be known which countries will be participating in clinical development and ultimately commercialization of the product. The stability and utility of retained serum or tissue samples is complicated by the diversity of the targets of the tests. For example, nucleic acids, antigens, IgG, and IgM.

2) Other tests in addition to those established as minimum requirements in Directive 2006/17/EC are required by some Member states[7&8]. There is no harmonization in the requirements for donor eligibility and testing between Member states. As cells and tissues may be used to manufacture a biologically active substance in a Medicinal Product (i.e., ATMP), according to GMP, the testing requirements described above may not apply (see EudraLex Volume 4, Annex 2). Further manufacturing steps are covered by Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67. Directive as last amended by Commission Directive 2003/63/EC (OJ L 159, 27.6.2003, p. 46)). However, in some countries (e.g. Germany), the requirements of Directive 2004/23/EC, as amended, have been transposed into the national drug legislation, hence, the donor testing requirements do apply to ATMP manufacture. This inconsistency among EU member states may become relevant when multi-EU-country clinical trials are performed and the donor material is procured in another country, where different donor[2] testing requirements do apply. Some country specific donor tests are only relevant to the country in which the donor resides (e.g. Chagas disease versus African sleeping sickness).

3) The tests must be carried out by a qualified laboratory, authorized as a testing centre by the competent authority in the Member State, using CE-marked testing kits where appropriate. The type of test used must be validated for the purpose in accordance with current scientific knowledge. It appears the principles anticipated by the EUCTD are similar to those of the medicines directive in that sponsors should be encouraged to use testing kits that are CE-marked. Where they are not CE-marked the sponsor is encouraged to get them CE-marked, or provide full validation data. There does not appear to be any central register of CE-marked approved testing kits in the EU. It is unclear what “where appropriate” means and to which extent equivalent kits, e.g., FDA approved/accredited testing kits can be used.

4) The US FDA requires FDA licensed, approved or cleared donor screening tests and the use of laboratories either Clinical Laboratory Improvement Amendments (CLIA) certified by the College of American Pathologists (GAP) or ISO certified by the Centers for Medicare and Medicaid Services. The certified laboratories do not have to be compliant with GMP requirements for the manufacture of medicinal products for human use, but they need to be compliant with health authority regulations that cover equivalent quality systems as the GMP. The Japanese Ministry of Health, Labour and Welfare (MHLW) notifications do not specify the donor test kits to be used.

5) Where such human cells or tissues are imported from third countries they must meet Community standards of quality and safety equivalent to those laid down in the Directive 2004/23/EC. It is unclear what “equivalent standards” mean. This aspect is of particular

relevance for tissue and cell based products which are of allogeneic origin (donor ≠ recipient) and the tissues and cells are procured within another jurisdiction, e.g., USA.

Details on transmissible disease testing requirements according to Annex II of the Directive 2006/17/EC, EU Member state additional requirements, the US FDA, and the Japanese MHLW notifications are provided in Table 1.

Table 1: Required tests in the EU, its Member States, the United States of America and Japan

Virus	**Tests**	**EU: Directive 2006/17/ EC**	**EU Member States: additional testing requirements** *(see Country code list below)	**USA: FDA (21 CFR 1271.85)**	**Japan: MHWL (PFSB notifications no. 1314, 0907-03, and 375/2014)[10]**
Human immunodeficiency virus (HIV), types 1 and 2	NAT[1]		DK, EE, IT, HU, PT, SK[4,5]	√	√
	Ag[2]		CZ, FR, MT, RO		
	Ab[3]	√		√	
Hepatitis B virus (HBV)	NAT		DK, ES, IT, HU, PT	√	√
	Surface and core Ag			√	
	Ab				
Hepatitis C virus (HCV)	NAT	√	DK, ES, IT, HU, PT	√	√
	Ag				
	Ab			√	
Treponema pallidum (syphilis)		√[6]		√	
Human T-lymphotropic virus (HTLV), types 1 & 2	NAT			√[7]	√
	Ag				
	Ab	√[8]	BG, DE, EL, ES, FR, HU, RO[9]	√	
West Nile	NAT			√	
Chagas				√	
Adult T cell leukemia	??				√
Parvovirus B19	??				√

[1] NAT = nucleic acid test; [2]Ag= antigen; [3]Ab= antibody; [4]SK= see country code list; [5]= HIV-1; [6] = A validated testing algorithm must be applied to exclude the presence of active infection; [7] = for specific cell types; [8] =HLTV-1 only and where risk; [9] = HTLV-1 only; [10] = Donation is also to be refused when necessary through tests for cytomegalovirus infection and EB virus infection

* Country Code List

Austria: **AT**,	Belgium:**BE**	Bulgaria: **BG**,	Croatia: **HR**,	Cyprus: **CY**,	Czech Republic: **CZ**
Denmark: **DK**,	Estonia: **EE**,	Finland: **FI**,	France: **FR**,	Germany: **DE**,	Greece: **EL**,
Hungary: **HU**,	Ireland: **IE**	Italy: **IT**,	Latvia: **LV**,	Lithuania: **LT**,	Luxembourg: **LU**,
Malta: **MT**,	Netherlands: **NL**,	Poland: **PL**,	Portugal: **PT**,	Romania: **RO**,	Slovakia: **SK**,
Slovenia: **SI**,	Spain: **ES**,	Sweden: **SE**,	United Kingdom: **UK**		

6) As cells and tissues may be used to manufacture a biologically active substance in a medicinal product for human use (i.e., ATMP), according to GMP, the testing requirements described above may not apply (see EudraLex Volume 4, Annex 2). Further manufacturing steps are covered by Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67. Directive as last amended by Commission Directive 2003/63/EC (OJ L 159, 27.6.2003, p. 46)).

3. Recommendations:

1. Clarification

   Clarification of testing requirements for cells and tissues used to manufacture Medicinal Products for human use (i.e., ATMPs) will be useful to reduce costs and uncertainty for the developers of these products. There are inconsistencies between EU member states and between Europe and the United States, and Japan. For countries such as Germany, where the European cell & Tissues Directives are transposed into the national drug laws there are issues for testing to be completed according to Good Manufacturing Practices.

2. Convergence

   As guidances should be based on scientific knowledge it is suggested that there can be a convergence of requirements. Initially, this would be to remove the differences between individual EU member states and national applicability of EU Directives. This could be followed by changes to enable the international development of allogeneic tissue-and cell-based products between ICH regions such as the EU, the US, and Japan.

   If there are changes in testing requirements or test methods, it is suggested that a risk-based approach can be taken to determine the actual risk to patients in the context of the donor risk profile.

   It would be beneficial to have test kits that meet the requirements of the European CE mark and US FDA. In addition, the requirements for the test facilities could be aligned according to common standards (e.g., ISO), which would allow the use of test kits and laboratories licensed/cleared and/or certified by health authorities of ICH member countries. These test facilities should have Quality Systems and operate to ISO 15189 Medical laboratories certified, but not to GMP.

3. Test methods

   A number of tests have been developed for blood banking and tissue donation. These tests identify the antigen (Ag) or antibodies (Ab) developed as the donor's immune response to the antigen. However, these tests may not be the most sensitive or may give false positive results requiring additional tests. Nucleic acid tests (NAT) are being developed that may provide rapid and more sensitive methods to detect these pathogens. It is highly recommended to enforce globally (e.g., through ICH, WHO) approved NAT tests in lieu of serological tests, unless otherwise justified, as they do not increase the risk of disease transmission to the patient or other people (potentially) coming into contact with the tissues/cells.

4. International standards

   For biologics and vaccines international standards have been created through organizations such as the World Health Organization (WHO), the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and International Alliance for Biological Standardization (IABS). These organizations have started to discuss the needs for standards for cell and tissue-based therapies, but have not addressed yet cell and tissue donation and testing specifically (reference Kyoto meeting[9]). Other regional economic organizations such Asian-pacific Economic cooperation (APEC) have started to look for regulatory convergence as a means to promote regional trade and have held a conference to specifically address the issues for cell based therapies (reference Singapore meeting[10]). We encourage all these forums to focus on the fundamental issue of donor testing.

4. Conclusion:

There is a need to harmonize the donor testing requirements among EU member states and globally to maintain high standards for patient safety while enabling the international development of transformational products, particularly for the treatment of multiple patients using the same tissue/cell source material. One way of regulatory harmonization is to align on the scientific principles of donor testing and converge on a common core of standards for the tests (NAT, where applicable, and unless otherwise justified) and test facilities that are developed and through organizations such as the WHO and ICH.

Within the guidances clarity is needed, in particular for the donor testing requirements for tissues and cells of allogeneic origin that are procured and used as source materials to manufacture medicinal products for human use according to GMP, where multiple patients are treated using the same tissue/cell source. The additional characterization, in-process and/or release testing according to GMP of cell and tissue based intermediates and/or medicinal products that have been more than minimally manipulated (e.g., expanded) should be more sensitive and controlled (i.e., according to ICH Q5A, than serological results and the inclusion of *in-vitro* and *in-vivo* adventitious tests should provide adequate assurance of detecting pathogens from the donor. This should be done on a risk-based approach.

5. References:

1. Link to Directive 2004/23/EC: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:102:0048:0058:en:PDF
2. Link to Directive 2006/17/EC: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:038:0040:0052:EN:PDF)
3. Link to Directive 2006/86/EC: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:294:0032:0050:EN:PDF
4. Link to Directive 2002/98/EC: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:033:0030:0040:EN:PDF
5. i) 21 Code of Federal Regulations Parts 210, 211, 820, and 1271 (eligibility determination for donors of Human Cells, Tissues, and Cellular and Tissue-Based Products);
   ii) Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Human Based Products HCT/Ps, August 2007
6. i) PMSB Notification No. 1314 dated December 26, 2000
   ii) PFSB/MHLW Notification No. 0907-03 (07/09/2012)
   iii) PFSB/MHLW Notification No. 1002/27: Partial Revision of the Standards for Biological Ingredients (MHLW Notification (KOKUJI) No. 375/2014 (02/10/2014)
7. Link to Commission report on Member State progress on implementation, 2009, which includes other tests in addition to those established as minimum requirements in the Directive 2006/17/EC: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2009:0708:FIN:EN:PDF
8. Link to Member State survey results, December 2008: http://ec.europa.eu/health/blood_tissues_organs/docs/tissues_responses_2008_en.pdf
9. Challenges Toward Sound Scientific Regulation of Cell Therapy Products IABS-JST joint workshop Kyoto March 8, 2014
10. 2014 APEC Harmonization Center- Health Sciences Authority Cell- and Tissue-based Therapeutic Products (AHC-HAS CTT) workshop 1-3 July 2014