



## European Union and Spanish Regulations on Quality and Safety of Tissues and Cells: Overview and Biovigilance

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### ABSTRACT

**Background.** The increasing therapeutic possibilities offered by tissues and cells during the last years, the existing discrepancies in regulation between Member States (MS), and the associated risks have led legislators in the European Union (EU) and its MS to establish a set of supranational standards that ensure quality and safety of human tissues/cells as well as processes related to donation, procurement, processing, and utilization. MS are under the obligation to incorporate the requirements of the European rules in their internal regulations.

**Regulation.** The regulations in the European Directives on tissues and cells range from the broad principles stated in Directive 2004/23/EC, to the detailed requirements described in Directives 2006/17/EC and 2006/86/EC. The aspects related to biovigilance were described in the latter. Spain has already complied with the obligation to transpose these Directives through the Royal Decree 1301/2006.

**Biovigilance.** Surveillance is a methodology often used in public health. The design of a surveillance system implies a decision-making process on the elements, procedures, and principles of the system. Regarding Spain, some of the elements have already been defined in the European or Spanish rules; however, other components of the biovigilance system have been discussed and developed in working documents outside of regulation.

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**T**HE INCREASING THERAPEUTIC possibilities offered by tissues/cells and the technical developments have led to a significant expansion in the last years.<sup>1,2</sup> Beyond the traditional implant, tissues and cells may be used for medical devices or tissue-derived biotechnological products. However, it must be borne in mind that the simple transfer of any biological substance from one individual to another entails certain disease-transmission hazards.<sup>3,4</sup> Such risks have to be controlled, the magnitude estimated, and the harmful effects prevented or minimized as far as possible.

Concern about the quality and safety of tissues came up in the European Union (EU) at the end of the last century. In 1998, the European Group on Ethics in Science and New Technologies to the European Commission reported an urgent need to regulate the conditions under which human tissues circulate within the European Market.<sup>5</sup> The discrepancies existing in regulations on quality and safety of tissues/cells between Member States (MS) were shown at a meeting of experts held in Porto in 2000. They consequently concluded there was an urgent need for a European

regulation. In a later conference in Málaga in 2002, co-organized by the Spanish Presidency of the EU and the European Commission (EC), more than 200 participants reaffirmed the need for a standard, supervised draft of a Directive, and provided guidance on its development with the immediate endorsement of the respective governmental representatives. Directives, in the EU setting, are a type of binding regulation addressed to MS, which have to transpose it, but are left to choose the way it fits within the framework of their internal legal orders.

The rule, developed under the provision of Article 152 of the Treaty, had to lay down high standards of quality/safety for the use of tissues/cells and had to be rigorous in light of current scientific knowledge, but flexible enough to allow MS to develop more stringent national regulations. In 2002,

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the EC submitted a proposal for a Directive to the Council of the EU and the European Parliament for approval through a codecision procedure, by which both institutions are at the same decision-making level. In March 2004, Directive 2004/23/EC set standards for the donation, procurement, testing, processing, preservation, storage, and distribution of human tissues and cells.<sup>6</sup> For the first time in the area of tissues and cells, a binding supranational, transparent, and sound regulatory framework had arisen, providing all citizens with the same minimum guarantees of quality and safety.

Beyond the overarching rules dictated in the Directive, the technical requirements had to be specified elsewhere, provided that any change would lead to a new long and laborious codecision process. For this purpose, two derived Directives, named “daughters” in contrast to the “mother,” were approved in 2006: Directive 2006/17/EC, developing technical requirements for the donation, procurement, and testing of human tissues and cells,<sup>7</sup> and Directive 2006/86/EC, regarding traceability requirements, notification of serious adverse reactions and events, as well as other aspects, including coding.<sup>8</sup> In Spain, these Directives were transposed into one Royal Decree. After consultation with a number of experts and bodies, it came into force in November 2006. Through this regulation, the EU requirements on quality and safety of tissues/cells were set in the Spanish context.<sup>9</sup>

## OVERVIEW OF THE LEGISLATION

Directive 2004/23/EC includes all processes from donation to application of human tissues/cells or their products, when both are intended for human application. For products covered by other directives, the 2004/23/EC applies only to donation, procurement, and testing. Tissues and cells intended for autologous use within the same procedure, blood, human organs, and substances of animal origin are outside its scope.

The obligations for MS dictated in Directive 2004/23/EC are shown in [Table 1](#). Some other regulated aspects are those related to donor selection and evaluation, provisions on the quality and safety of tissues/cells, exchange of information, as well as reports and penalties.

Whereas Directive 2006/17/EC details thoroughly techni-

cal aspects related to donation, such as selection criteria, laboratory tests, or processes related to distribution and reception of tissues and cells, Directive 2006/86/EC focuses on the implementation of elements related to biovigilance, such as traceability, notification, exchange of information, or coding.

By the Spanish Decree the contents of the 3 Directives to the Spanish health care system have been transposed and organized as follows: (1) donation and procurement; (2) processing, storage, and distribution; (3) application of tissues/cells; (4) information, follow-up, and biovigilance systems; and (5) other related aspects. Additionally, included in the respective annexes were thorough information on selection, procedures, minimum information required for the traceability system, coding, and notification sheets for adverse events and reactions.

## BIOVIGILANCE

Biovigilance may be defined as the surveillance of adverse events and reactions associated with the utilization of tissues and cells. Methodologically, surveillance is a public health activity, defined as the systematic and continuous collection, analysis, interpretation, and dissemination of health data, seeking to reduce morbidity and mortality and to improve the health of the population. It is based on careful vigilance. Its objectives are to ascertain and monitor the frequency and distribution of incidents, and more importantly, to prevent and minimize the risk of occurrence of the events monitored.<sup>10</sup>

A surveillance system is a set of interconnected elements and activities that participate in the achievement of the objectives of the system itself. The design of one of those systems requires the definition of some elements, procedures, and principles. Additionally, the involvement of external factors is of great interest; eg, appropriately coded registers, being essential for the identification and location of patients or tissues.

Whereas biovigilance has not been specifically mentioned in the EU Directives, some elements of a biovigilance system have been defined and required. The Spanish Decree has a chapter on information, follow-up, and biovigilance systems, treating the latter as a reporting system for adverse events and reactions. Some of the elements regulated in the Directives and the Spanish Decree are: (1) definitions of serious adverse events (SAE) and reactions (SAR), as shown in [Table 2](#), to be used as the case-definition; (2) notification of SAEs and SARs, with requirements for systems to report, investigate, register, and transmit information about SAEs and SARs; (3) traceability of all tissues and cells from donation to recipient and vice versa; (4) a coding system for the identification of tissues and cells; (5) designation of a Competent Authority responsible for the process and for communication with the EC, being appointed the Organización Nacional de Trasplantes as the Competent Authority for Spain; (6) a biovigilance network (in Spain, the organ donation and transplantation

**Table 1. Obligations of Member States Laid Down in Directive 2004/23/EC**

Designation of a Competent Authority
Supervision of human tissue and cell procurement
Accreditation, designation, authorization, or licensing of Tissue Establishments and tissue and cell preparation process
Implementation of a system of inspections and control measures
Implementation of a system of traceability
Guarantee on quality and safety of imported/exported human tissues and cells
Register of Tissue Establishments and reporting obligations
Notification of serious adverse events and reactions

**Table 2. Definitions of Serious Adverse Events and Reactions Laid Down in Directive 2004/23/EC**

	Definition Laid Down in Directive 2004/23/EC
Serious adverse event	Any untoward occurrence associated with the procurement, testing, processing, storage, and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling, or incapacitating conditions for patients, or which might result in, or prolong, hospitalization or morbidity
Serious adverse reaction	An unintended response, including communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating, or which results in, or prolongs, hospitalization or morbidity

coordination network has been designated the biovigilance network); and (7) confidentiality and data protection (in Spain, access is restricted to authorized staff).

Other elements of the system, such as the procedures, the roles within the working network, or the principles governing the system, have been developed in working documents and submitted to approval outside of the regulation.

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