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European Definitions, Current Use, and EMA Stance of Platelet-Rich Plasma in Sports Medicine

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Abstract

Platelet-rich plasma has been the focus of much attention over the last few years as an appealing biological approach to favor the healing of tissues otherwise doomed by a low healing potential. In Europe, the regulatory framework concerning the blood system is currently disciplined by Directive 2002/98/EC of the European Parliament and Council of January 27, 2003, which sets out quality and safety rules for collecting, controlling, processing, preserving, and distributing human blood and its components, acknowledged in the various States of the Union with internal regulations. This lack of homogeneity in the European legal landscape will probably lead the Community legislature to intervene in the near future, to even out the "rules of engagement" of this peculiar class of biomaterials.

Keywords
- PRP
- European regulation
- European definitions
- sports medicine

Platelet-rich plasma (PRP) has been the focus of much attention over the last few years, as an appealing biological approach to favor the healing of tissues otherwise doomed by a low healing potential. Since PRP is a blood-derived product, its use is strictly regulated in Europe, to ensure the control of all the aspects related to preparations, storage, and distribution, and therefore the quality and safety of PRP products.

This article aims to focus on the regulatory framework related to the products derived from the manipulation of whole blood (PRP) through medical devices for separation, without specifying the regulations concerning the development and marketing of the devices (generally falling in the category of medical devices within the European Directive 93/42), which often have completely different risk categories due to the heterogeneity of manufacture, assembly, and operating instructions, and require specific and nonuniform regulatory pathways for obtaining the CE mark.

The Current Reference Regulatory Framework in Europe

In Europe, the regulatory framework concerning the blood system is currently disciplined by the Directive 2002/98/EC of the European Parliament and Council, January 27, 2003, which sets out *quality and safety rules for collecting, controlling, processing, preserving, and distributing human blood and its components*, acknowledged in the various States of the Union with internal regulations.

The salient contents of the European regulatory framework aim to ensure, at community level, a high level of protection of human health.

The fundamental principles of the text are the following:

- *License for hematological centers*. Member states must ensure that activities concerning the collection and control of human blood and its components are performed only by

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hematological centers that have obtained a designation, authorization, accreditation, or a license for this purpose from the appropriate authority, recognized by each member state according to its own institutional setup.

- *Nominating a head of the transfusion service*. The head of the transfusion service, under his/her own responsibility, will have to, among other things, ensure that each unit of blood or blood product, for any intended use, be collected and controlled and, if intended for transfusion, be processed, preserved, distributed, and assigned in compliance with the regulations in force.
- *Qualified staff*. The staff who participates in collecting, controlling, processing, preserving, distributing, and assigning human blood and blood products must have the qualifications required by the regulations in force to carry out these functions and receive, in due time, adequate professional training, periodically updated.
- *Quality system*. Member states must adopt the necessary measurements so that the transfusion service and the collecting units form and maintain a quality system based on the principles of good practice and according to the regulations in force.
- *Using a rigorous penalty system* to stop nonauthorized transfusion services.

The European Commission's Position

In the Summary Report following the *Meeting of the Competent Authorities on Blood and Blood Components* (held on October 11–12, 2012, in Brussels) concerning PRP, the Commission indicated that after consultation with the legal service SANCO (Directorate-General for Health and Consumer Protection), the procedure should fall within the scope of the directives on blood, although the appropriate national authorities have highlighted how in practice it is difficult to bring this procedure fully in line with what is envisaged by the 2002 Directive. The legal service SANCO has therefore reported that this procedure will in future be the subject of specific and unitary regulations by the European Union. This position was confirmed in the *Meeting of the Competent Authorities on Blood and Blood Components* (held on April 17–18, 2013, in Brussels) and it is one of the audited annual regulatory agenda of European authorities competent in the field of organ and tissues.

Execution of the Regulations in Italy

From a legal point of view, we can clarify some salient points that qualify the procedure for employing blood components for noninfusion/transfusion use (topical).

The term "topical" is equivalent, from a legal point of view, to "noninfusion/transfusion" and indicates all therapeutic applications in which blood components are not transfused into the patient but are used directly in the pathologic area through different ways (intra-articular/deep-tissue injection in orthopedics, cutaneous in dermatology, subcutaneous in plastic surgery, etc.).

Blood Components, Non-Hemoderivatives

A big advantage of this procedure is to obtain the final product by harvesting a very limited amount of blood from the patient. With that in mind, the preparation of concentrates or platelet gels is not considered as the production of blood derivatives, but as fractionating the blood itself by simple and/or physical means to obtain blood components.

Currently, it is technically possible, once authorized by the competent/specific authorities, for any orthopedic surgeon to prepare concentrated platelets, even in an outpatient setting, by using appropriate machines, in some cases in a closed circuit or more commonly in asepsis, with the CE mark, that can centrifuge and/or filter the blood harvested from the patient and separate completely autonomously the plasma part rich in platelets for therapeutic use.

Safety, Use, and Preparation (Minimum Manipulation)

Minimum manipulation refers to blood components that do not interact with other drugs and are prepared quickly. The only risk, in the case of autologous donors, can be *malpractice* in the preparation system. Concerning their use, in the case in question the blood components have a topical therapeutic indication and therefore beyond the classic infusion/transfusion administration.

Concentrated platelets are, without doubt, prepared by simple physical means (centrifugation, separation), provided that the practice itself is not used for experimental purposes or somatic cell therapy. This is also supported by two more considerations:

1. The manipulation in question can be considered minimum (even in the hypothesis where there is not a simple centrifugation of the autologous blood but the platelet concentrates are made into a gel by adding autologous cryoprecipitate, sterile calcium gluconate, and batroxobin).
2. These manipulations do not produce any cell proliferation because the platelets are cell elements without nucleus, which release cytokines after shape modifications, albeit to a lesser extent, in all apheresis procedures.

Reference Regulatory Scope

The products in question are blood products.

The Committee for Advanced Therapies (CAT) meeting on November 13, 2009, seems to have identified "fresh and freeze-dried thrombocytes isolated from autologous or allogeneic blood" as "products, intended for wound healing in orthopaedic and dental surgery" and these products were not considered by CAT as advanced therapy medicinal products.

Reference Regulatory Framework

The regulatory framework relevant to the blood system is currently regulated by the following:

- By the decree of October 21, 2005, no. 219 (new discipline for transfusion activities and national production of blood derivatives).

- By the almost contemporary decree of August 19, 2005, no. 191 (implementation of Directive 2002/98/EC that sets out the rules of quality and safety for harvesting, controlling, processing, preserving, and distributing human blood and its components), subsequently replaced by decree of December 20, 2007, no. 261 (revision of decree of August 19, 2005, no. 191, bearing implementation of Directive 2002/98/EC that sets out the rules of quality and safety for harvesting, controlling, processing, preserving, and distributing human blood and its components).
- By the Health Ministry Decree of March 3, 2005. It is the most important document, on a technical and operative level, concerning the preparation and use of blood components: although it was issued in implementation of the previous law 107/90, it is still in force as it is expressly stated in Law 219/2005, which states that the previous implementing decrees remain in force until they are replaced by new ones.

While the law of October 21, 2005, no. 219 and the decree of December 20, 2007, no. 261 refer to blood system in general, the decree of March 3, 2005, defines the rules for the preparation of blood components, and these rules can be used both by the blood transfusion service and in the "remote" preparation.

Operative Aspects: The System of Authorization

The manipulation of blood is by law (219/2005) restricted to transfusion services. The Transfusion Services are accredited public structures, normally identified in hospitals, which are reserved for all activities concerning the collection, the storage, the handling, and the allocation of blood and blood components.

Nevertheless, it has been recognized, from a legal point of view, that the *service* supplied by the transfusion services can also be extended to the "remote" outpatient preparation of blood components for topical autologous use by ad hoc agreements that allow:

- The service to keep control over the remote processing of blood components, including traceability, meaning registration of the procedure.
- Doctors and/or surgeons to provide the patient with a rapid effective service and doubtless therapeutic as well as logistical advantages (no need for predonation, fresh product, and not frozen, reduced harvesting of blood).

The agreement between physicians and transfusion structures allows the physician to the ambulatory preparation of blood components for topical use under the control of the competent Transfusion Service: any manipulation of blood components without the required authorization constitutes a criminal offense.

It is interesting to notice that, while from a certain point of view the regulation in Italy is easier, because the use of outpatient PRP without authorization and agreement with Transfusion Center is never legal, more heterogeneous and complex is the situation of other European countries.

Implementation of the Regulations in Spain

Spain has implemented Directive 2002/98/EC by Royal Decree 1088/2005 of September 16, 2005, which indicates the technical requirements for the donation, processing, and use of whole blood and blood components.

From a technical point of view, platelet separation must be performed in closed circuit or at least in aseptic systems (Article 12). It is interesting to note how all procedures concerning the manipulation of blood intended for transfusion are under the control of blood transfusion centers (Center de Transfusión Sanguínea, Articulo 29), but in the case of special procedures (autologous, intraoperative use, with small amounts for specific protocols of treatment), the Comité Cientifico para la Seguritad Transfusional (CCST) declares that these procedures may not come under the hemotherapy practices included in the above-mentioned regulations (opinion CCST in response to a request for clarification of May 10, 2004).

Implementation of the Regulations in France

In France, the implementation of the "Blood System" is down to the Direction générale de the santé (DGS), whereas the system of haemovigilance is the responsibility of Afssaps (Agence française de sécurité sanitaire des produits de santé replaced by the ANSM Agence nationale de sécurité du médicament et des produits de santé since March 1, 2012) and is based on a network of blood transfusion centers (over 800 throughout France).

The system of transfusion control mainly concerns the Produits Sanguins Labiles (PSL, Labile Blood Product) products obtained from blood donors intended to be transfused into a patient for therapeutic purposes (article L1221–8 of the Code del la Snteé Publique, amended by the law 2011–2012 del December 29, 2011, Article 5). This normally involves whole blood, plasma, and blood cells of human origin: the list and the properties of PSLs are determined by the ANSM after consultation with the Etablissement français du sang (EFS), a public institution with numerous advisory functions relating to the use of human blood.

That means that, whereas stable preparations for blood transfusions are considered to all intents and purposes as drugs, PSLs (including blood components for topical use) are not regulated equally but assessed and authorized case by case.

Implementation of the Regulations in Germany

In Germany, the law on blood components considers them as medicinal products and therefore requires authorization to be placed on the market according to the German medicinal product act (AMG, ARZNEIMITTELGESETZ), which is the law of reference in this sector. More in detail, the systems for blood processing are considered as Medical Devices in Germany, but the product of the processing is a human tissue

and falls within the general discipline of the AMG of the Federal Republic of Germany.

The central organization that releases the authorization is the Paul-Ehrlich-Institut (PEI), the highest Federal Authority inside the German ministry of health that oversees the activities of the appropriate Regional Authorities of the German federal state ("Laender").

The transfusion of blood components is regulated by the Germany Transfusion Act (Transfusionsgesetz; TFG), in particular section 18 of said act: *The Hemotherapy Guidelines are particularly important.*

The Case of Switzerland

Switzerland is not a member of the European Union, but there are similar regulations concerning the blood system as the principles expressed in Directive 2002/98/EC.

In Switzerland, the Law on Therapeutic Products (LTP) applies to synthetic and biotechnological drugs, vaccines, medical devices, implants, diagnostics, and blood products, whose preparation must follow the standards envisaged for the preparation of drugs (in a similar way to that envisaged in Germany). The regulatory authority that controls and governs the sector is Swissmedic, which has authority throughout the Swiss cantons.

In accordance with Article 58 of the Swiss Law on Therapeutic Products, Swissmedic is responsible for haemovigilance: any institution authorized to handle blood and blood products (e.g., blood transfusion services) must have a reporting procedure and appoint a person who is in charge of haemovigilance and reports adverse incidents that occurred during the production and distribution of the products.

PRP Use in Europe: Summary

The analysis of the European regulations, despite coming from the same directive, allows us to draw the following conclusions on the use of blood products for topical use:

- There is a general European principle, according to which blood components can be used after checking the national authorities responsible for transfusion activities.
- In Italy, the principle does not allow exceptions, and blood components for topical use (considered as blood products) are always under the responsibility of the Blood Transfusion Service, regardless of the amount, type, and protocol processing of clinical use.
- In other European countries, in some cases, blood components are considered as blood products or, in other cases, as medicines. However, depending on the amount, the processing, and clinical protocol, in some cases, they can be used in a less restrictive manner, under the control of the physician. Unlike in Italy, the physicians will submit the protocol to the regulatory authorities of each country to get advice on how to use specific blood components and to determine if the authorization is required or if the therapy can be considered an act to be performed freely under the control and responsibility of the physician.
- This lack of homogeneity in the European legal landscape regarding the management of the product obtained from whole blood processing will probably lead the Community legislature to intervene in the near future, to even out the "rules of engagement" of this peculiar class of biomaterials.

PRP technologies are being offered to European clinicians due to their CE mark, but individual European countries are treating the use of these devices differently. For example, while in Italy the manipulation of the blood is always under the responsibility of the Blood Transfusion Service and can be delegated to individual physicians only through an authorization, in other countries, in some procedures that depend on the protocol used by the doctor (and which may vary depending on the type of use, the amount of blood, the system of preparation, etc.), it is possible the ambulatory use under the direct responsibility of the physician.

In the setting of European countries, there is a general rule but in each country the "legal" way to use depends on the protocol and thus the regulation ends up being heterogeneous and often complex, sometimes requiring specific authorization or the need of other clinicians besides the surgeon, such as transfusion services, to be involved in the processing steps. These requirements make it difficult for clinicians in certain countries to utilize PRP within their operative and clinical practices.

It would be helpful for all the countries that accept a CE mark for a device to function in the same way with respect to processing specifications/standards, simplifying, and favoring the use of PRP. There is a very large difference between using a blood product such as a therapeutic platelet infusion to treat thrombocytopenia and using PRP for bone grafting procedures or using PRP to treat something like osteoarthritis or tendonitis. Thus, it is desirable that "drug-centric" European regulatory tendency for biological products of this historical moment, as reflected by the recent reflection paper EMA/CAT June 2014, will lead to a homogeneous regulatory framework to simplify and favor the use of PRP for Sports Medicine.

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