CellPress

Closing regulatory gaps: new ground rules for platelet-rich plasma

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The Spanish Agency of Medicines and Medical Devices (AEMPS) has drawn up a comprehensive report and resolution that regulates for the first time the use of platelet-rich plasma (PRP) as a human-use medicinal product. This regulatory framework offers emerging challenges to adapt the use of PRP to the new requirements of safety and efficacy. The heterogeneity of the different products can hinder their regulation, which today differs substantially in the different worldwide regulatory frameworks.

Background on PRP therapies

Recent advances in cell biology and engineering, aided by new discoveries in other fields, are making possible new therapeutic strategies in regenerative medicine. For example, PRP therapies are being increasingly used in various medical fields ranging from dentistry to dermatology, traumatology, and, more recently, ophthalmology and had an estimated global market of US$45 million in 2009, projected to grow to US$120 million in 2016 [1]. PRP therapies are all based on the preparation and use of plasma obtained from peripheral blood that has been enriched for platelets above the physiological level [2]. Platelets contain numerous bioactive molecules, including growth factors that play an important role in the healing of injured tissue. Additionally, the plasma fraction contains a pool of molecules that contribute to the regeneration of tissues, such as fibronectin and vitronectin [3]. PRP technology can also be used in *ex vivo* procedures for the expansion of stem cells, replacing fetal bovine serum (FBS) as a culture supplement [4], as demonstrated in a recent clinical trial involving the expansion of adipose-derived stem cells [5].

However, there is no single standard regarding the preparation or composition of PRP, which has led to a lack of consensus on the very definition of the term. There are differences between the various commercial PRP kits regarding the amount of platelet enrichment, the presence of leukocytes and erythrocytes, and the activation mode. The different types of PRP may thus yield different clinical outputs and trying to regulate PRP technology will prove to be challenging.

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Classifying PRP as a medicinal product in Spain

Recently, AEMPS has drawn up a comprehensive report [Spanish Agency of Medicines and Medical Devices (2013) *Report/V1/23052013. The Spanish Agency of Medicines and Health Care Products' Report on the Use of Platelet-Rich Plasma. Informe de la Agencia Española de Medicamentos y Productos Sanitarios sobre el Uso de Plasma Rico en Plaquetas* (http://www.aemps.gob.es/medicamentosUsoHumano/medSituacionesEspeciales/docs/PRP-AEMPS-DEF-mayo13.pdf)] and a subsequent resolution [Spanish Agency of Medicines and Medical Devices (2013) *Resolution Establishing the Classification of Non-replacement Therapeutic Use of Autologous Plasma and its Fractions, Components or Derivatives as a Medicinal Product for Human Use to Meet Specialised Needs. Resolución por la que se Establece la Clasificación del Uso Terapéutico no Sustitutivo del Plasma Autólogo y sus Fracciones, Componentes o Derivados, como Medicamentos de Uso Humano para Atender Necesidades Especiales* (http://www.aemps.gob.es/legislacion/espana/medicamentosUsoHumano/docs/medEspeciales/resolucion-PRP.pdf)] that regulates for the first time the use of PRP as a human-use medicinal product. To establish this classification, AEMPS has considered, among other elements, the composition of PRP, its mechanism of action, and medical guidelines, along with the definition of a medicinal product at both the Spanish level [Official State Gazette (2006) *Law 29/2006, of July 26th, on the Guarantees and Rational Use of Medicines and Healthcare Products, BOE 178, of July 26th)* (http://www.boe.es/buscar/pdf/2006/BOE-A-2006-13554-consolidado.pdf)] and the European level [Official Journal of the European Communities (2001) *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* (http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_cons/dir2001_83_cons_20081230_en.pdf)]: 'any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis'.

AEMPS has clarified that, although it is a medicinal product for human use, obtaining PRP does not involve an industrial process and therefore PRP cannot be considered an industrially produced medicinal product. However, AEMPS has framed PRP outside the category of advanced-therapy medicinal products, according to the

Box 1. Guarantees required for the use of PRP in Spain[*,†]

Guarantees of quality

As for any other medicinal product, it will be necessary to establish minimum quality guarantees throughout the manufacturing process. AEMPS and the various regional regulatory agencies will agree to a common policy on this issue. The regulation also differentiates between 'open-technique' and disposable (closed system) kits. The first will require more comprehensive quality controls and inspections. Disposable kits must always be medical-device CE marked, indicating that they comply with European directives, and should be used following the manufacturer's instructions.

Guarantees of efficacy

AEMPS recognizes that PRP is used in several areas of medicine, but the agency has no clear evidence of its efficacy in all of them. Therefore, AEMPS will create a report including applications for which there is clear evidence of efficacy, classifying the different applications of PRP in three categories depending on the available evidence: pathologies in which there is sufficient evidence to recommend the treatment; those that have been shown to have a negative benefit–risk balance and will not be recommended for use; and those requiring further evidence.

Guarantees of traceability

One of the particular characteristics of this therapy is its biological origin, and therefore the possibility of transmission of disease must be present despite its autologous character. Prescribing physicians will have to adopt specific control, supervision, and traceability measures to prevent the transmission of infectious diseases. In this respect, the Spanish legislation has issued several royal decrees on blood donation, autologous donation, and autotransfusion that must be taken into account in ensuring the safety of the procedure for obtaining PRP.

Guarantees of pharmacovigilance

Another highlight of the AEMPS report is the duty to promptly notify to the competent pharmacovigilance authority of each regional government any suspected adverse reactions as a result of treatment with PRP. Thereby, the rapid location of defective or contaminated lots would be ensured in the same way as for a conventional medicinal product, significantly increasing treatment biosecurity by establishing a registry of adverse events.

Guarantees of information

All medicinal products must have a summary in which the characteristics of the product are detailed and a package leaflet with basic information and instructions for the patient. However, due to its particular features, PRP has no a registered summary of product characteristics. Despite this and according to the new regulations, the patient should receive a minimum amount of information before any treatment, ensuring that the product meets the quality requirements, including its recognized efficacy, the pros and cons compared with other treatments, and any potential risks and/or side effects.

[*]Spanish Agency of Medicines and Medical Devices (2013) *Report / V1 / 23052013. The Spanish Agency of Medicines and Health Care Products' Report on the Use of Platelet-rich Plasma. Informe de la Agencia Española de Medicamentos y Productos Sanitarios sobre el Uso de Plasma Rico en Plaquetas* (http://www.aemps.gob.es/medicamentosUsoHumano/medSituacionesEspeciales/docs/PRP-AEMPS-DEF-mayo13.pdf).

[†]Spanish Agency of Medicines and Medical Devices (2013) *Resolution Establishing the Classification of Non-replacement Therapeutic Use of Autologous Plasma and its Fractions, Components or Derivatives as a Medicinal Product for Human Use to Meet Specialised Needs. Resolución por la que se Establece la Clasificación del Uso Terapéutico no Sustitutivo del Plasma Autólogo y sus Fracciones, Componentes o Derivados, como Medicamentos de Uso Humano para Atender Necesidades Especiales* (http://www.aemps.gob.es/legislacion/espana/medicamentosUsoHumano/docs/medEspeciales/resolucion-PRP.pdf).

definition given by the EU [Official Journal of the European Union (2007) *EC / 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* (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF)]. From a regulatory perspective, excluding PRP therapy from the category of advanced therapies could clearly facilitate, from the regulatory viewpoint, its use both intraoperatively and on an outpatient basis.

For AEMPS, there are three direct consequences of the inclusion of PRP in the category of human-use medicinal products. First, according to Article 5 of Directive 2001/83/EC of 6 November 2001 [Official Journal of the European Communities (2001) *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* (http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_cons/dir2001_83_cons_20081230_en.pdf)] referring to these types of products, the use of PRP must be prescribed by a doctor, dentist, or podiatrist only, within their respective competencies, and not by any other healthcare or non-health-care professional. Second, only doctors, dentists, and podiatrists with the appropriate qualifications and experience of the treatment may prescribe PRP therapy. These physicians must always use the appropriate equipment and instruments and PRP can be used only in authorized healthcare facilities and centers in accordance with the current regional government regulations. Third, as with any other medicinal product available only on prescription, advertising it to the general public is prohibited.

The AEMPS report indicates that a case-by-case authorization is not required. However, a physician who prescribes the treatment must ensure regulatory compliance with the competent inspection authorities. This legal framework enables the use of PRP therapies with all of the guarantees of quality, efficacy, traceability, and pharmacovigilance (Box 1).

Emerging challenges

There remain several key challenges in the development and evolution of the regulation of PRP products in Spain. It will be necessary to have a list of approved medical devices and the medical applications for which their use is authorized. It should be noted that systems for obtaining PRP differ and that their different compositions may influence the clinical output. Thus, the presence of leukocytes in the plasma, the platelet enrichment, and the method of activation and release of growth factors will differ for each system. Although the systems can be grouped by any of the proposed classifications [6], it is difficult to generalize clinical results for one particular system to the rest.

Following the principles of the new Spanish regulations, the approval of a PRP commercial system for the treatment of a given pathology does not mean that automatically all PRP systems may be authorized to treat that disease. This is due to the fact that the characteristics of other PRPs could differ from those of the approved PRP and this could affect the clinical outcome of the treatment. On the one