Farmaindustria's position on the substitution of biological medicines

Farmaindustria has acknowledged a legal report from Castilla la Mancha Health Service (SESCAM) which maintains that the substitution rules for biological medicines would only affect medicines within the remit of pharmacies meaning therefore, "the substitution of this kind of medicine in hospitals constitutes a perfectly legal option."

Before revealing Farmaindustria's position on this matter, we first need to be reminded about the importance that biosimilar medicines' entry into the market has for the sustainability of the Spanish national healthcare system; once the IP rights of the original have expired, so that savings in public expenditure can be generated. Nevertheless, the entry of biosimilars shall be undertaken with an appropriate respect for the technical regulation derived from these products' special characteristics.

Likewise, it is advisable to specify three concepts, highlighted in several scientific works about biologic medicines, which contribute in adequately defining the use of said medicines: prescription, interchangeability and substitution.

- *Prescription*: *decision made by the physician to determine which medical treatment is the most appropriate for a certain patient*. In Spain, as in many other countries, the prescription of biological and biosimilar medicines can only be made by doctors.
- *Interchangeability*: possibility to exchange, with any patient, a certain medicine for another one because both of them have the same clinical effect (in Spain, medicines considered to be legally interchangeable comprise the so-called homogenous groups)
- *Substitution*: *dispensing a certain medicine for an interchangeable one without previous consultation from the prescribing doctor*. In Spain, in order for pharmacists

to be able to undertake the substitution, it is necessary that said medicine is deemed legally interchangeable.

Hence, from a clinical point of view, biological medicines can have different clinical effects, thus they cannot be considered interchangeable. Interchangeability is a trait which is related to the intrinsic complexity of medicines and would require the presentation of accrediting documentation before the medicines' regulatory agencies. This is so acknowledged by the EMA in Europe – and the Spanish Medicines Agency (AEMPS), whereas the FDA will do so based on a case by case analysis, though this has not been the case for the moment for any authorized biosimilar medicine.

In this context, it is appropriate to clearly state that, according to Spanish in-force legislation, biological medicines are not interchangeable and do not admit substitution. This comes from Order SCO/2874/2007, September 28th, and informative Note from the Spanish Medicines and Medical Devices Agency from 24/04/2009, about medicines which can be the object of substitution by other medicines with the same active ingredient without the previous explicit authorization from the prescribing doctor.

On the other hand, from a legal point of view, taking into account the specific characteristics of biological medicines, all of them should bear the condition of "singularized medicines". They are subject to additional monitoring, as far as pharmacovigilance is concerned, and are identified by an inverted black triangle in the medicines' technical sheets and leaflets (▼ Medicines under additional monitoring). The AEMPS states, "the aim of identifying medicines subject to additional monitoring, is so that healthcare professionals, and patients, can identify those medicines that are more subject to post-authorization safety monitoring than other medicines, due to limitations in their clinical practice." Therefore, the law forbids them to be prescribed using their international non-proprietary name (art. 3 from RD 1718/2010, of medicine prescription, in its wording by RD 81/2014), neither can an adverse reaction be

noted without expressly indicating their brand name and manufacturing lot number (art. 5 from RD 577/2013, of pharmacovigilance).

All of the above does not hinder duly authorized biological medicines, including biosimilars, from being prescribed with absolute normality in all their approved indications; nothing should refute the freedom of Administrations to undertake public tenders for the purchase of said medicines. In any case, it shall be guaranteed in a real and effective manner that any change is made according to the doctors' intervention, such as stated by Ruling 394/2015 from the Public Procurement Administrative Court of the Andalusian Government, which is well reflected in SESCAM's report, "in those clinically justified cases in which it was necessary to prescribe a different brand name than the one allocated, the doctor may do so without further limitations".

The latter is also fundamental if one considers a potential additional question; who would be liable for civil and, where appropriate, criminal liability, in the event of an automatic substitution (without intervention of the prescribing physician) of a biological drug by a non-interchangeable drug that would have negative consequences for the patient.

In conclusion, the Spanish Government itself has already stated in a answer to a Parliamentary question regarding the limitations to interchangeability and substitution of biological medicines (BOCG, series D nº 472, June 5th 2014, page 345) that, "biosimilar medicines are biological medicines and, as such, are not able to be exchanged, nor substituted when being dispensed without the previous knowledge of the prescribing doctor":