Biologicals and Biosimilars: Gaps in the Pharmacovigilance System in Portugal

Medicamentos Biológicos e Biossimilares: Descontinuidades no Sistema de Farmacovigilância em Portugal

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ABSTRACT

Introduction: Biological and biosimilar medicinal products have specific characteristics that call for a closer monitoring of their safety profile. Since the current legal framework stems from both European and national regulations, some gaps in the operational field may be expected. The goal of this paper is to identify these gaps and propose changes to the current information systems and pharmacovigilance regulations.

Material and Methods: A qualitative analysis of current pharmacovigilance regulatory framework and supporting information system was conducted.

Results: Current pharmacovigilance system does not seem to vouch for the safe use of biologicals and biosimilar drugs. The gaps found in reviewed materials may be attributable to their lack of specificity for biopharmaceuticals.

Discussion: Biologicals therapy presents specific determinants related with the drugs, prescription, and traceability, without replication in any other segment of the pharmaceutical market. They are able to shape their safety profile.

Conclusion: The existing pharmacovigilance's regulatory framework should be adjusted in order to improve the safety related with biopharmaceutical therapy. Some intervention measures are proposed.

Keywords: Adverse Drug Reaction Reporting Systems; Biological Products; Biosimilar Pharmaceuticals; Drug Monitoring; Pharmacovigilance; Portugal

RESUMO

Introdução: A monitorização da segurança associada aos medicamentos biológicos e biossimilares exige um sistema de informação alinhado com o enquadramento regulamentar. Tendo em conta que podem ocorrer descontinuidades entre a regulamentação europeia, nacional e a respetiva tradução operacional, importa pesquisar e identificar essas lacunas.

Material e Métodos: Foi desenvolvida uma análise qualitativa dos suportes legais vigentes em julho de 2016 ao nível europeu e nacional, com foco na farmacovigilância. Desta análise decorreu a caracterização operacional do sistema em Portugal.

Resultados: Foram identificadas zonas de descontinuidade no âmbito do sistema de farmacovigilância em Portugal, pela ausência de especificidade para os medicamentos biológicos e biossimilares.

Discussão: A segurança associada à terapêutica biológica apresenta determinantes específicos relacionados com os medicamentos, prescrição e traçabilidade, que não encontram replicação nos outros segmentos do mercado farmacêutico.

Conclusão: Com base nas lacunas identificadas, são apresentadas propostas de intervenção com o objetivo de incrementar a segurança associada à utilização clínica de medicamentos biológicos e biossimilares.

Palavras-chave: Biossimilares; Farmacovigilância; Medicamentos Biológicos; Monitorização de Fármacos; Portugal; Sistemas de Notificação de Reações Adversas a Medicamentos

INTRODUCTION

Biological and biosimilar medicines are very complex and variable molecules or mixture of molecules affecting both their safety and efficacy profile. These factors should also be considered regarding interchangeability and switching. Therefore, benefit to risk ratio monitoring must be ensured, considering that some frontiers of instrumental discontinuity may exist within the alignment between regulatory and operational domains which must be identified and rectified. The specific information on biological and biosimilar medicines may not be adequately addressed by the pharmacovigilance system, due to its universal nature; this study aimed at the identification and characterisation of such information.

MATERIAL AND METHODS

This was a qualitative analysis based on the national and European legislation as well as on the legal reports issued by the regulatory authorities. The available coded information from the website of the Portuguese national authority of medicines and health products (INFARMED),

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the public institutions governed by the Portuguese Ministry of Health and the European Medicines Agency was used and search was restricted to the current regulation on pharmacovigilance. In a subsequent stage, the content of the latter was analysed and the information specifically regarding biological and biosimilar medicines has been selected. In addition, regulation on converging areas with this domain was considered: counterfeit tracking, traceability and trans-frontier healthcare. An assessment aimed at characterising the operationalisation of regulatory determinations and identifying the information flows and communication systems used for the prescription and dispensing of biological and biosimilar medicines, as well as the Portuguese system of adverse event reporting and record has been subsequently carried out. Information was restricted to the applicable legislation by July 2016, regardless of the year when it was published.

RESULTS

Biological, biotechnology-derived and biosimilar medicines

Biological medicines consist of one or multiple biologically derived active ingredients. Originator biologics approval is based on comprehensive technical and scientific documentation in terms of quality, safety and efficacy. Biosimilar medicines are usually approved upon a brief procedure in which similarity (although not the equivalence) to a pre-existing originator biological medicine is ensured. Therefore, comparability studies provide the evidence needed to support similarity in terms of quality, safety and efficacy, ensuring that biosimilar medicines provide the same efficacy and safety as originator biologics.[1]

Biotechnology-derived medicines are produced by fermentation of cells usually modified by recombinant DNA technology for the expression of the active substance. Biological medicines can be obtained following a biotechnological pathway or made from living organisms. In the first case, bioreactor production may induce heterogeneities between medicines from different manufacturers or between different lots of the same medicine to which adverse events are related, while in the second case inter-individual rather than intra-individual heterogeneities are anticipated, due to individual homeostatic control. Biologics protein base, in addition to high molecular weight and biologically-based materials used for production may determine for an intrinsic variability leading to changes in the safety and efficacy profile that must be considered and therefore making this segment of medicinal products crucial in terms of pharmacovigilance.[2]

Models of accessibility to therapy

Medical prescription is the instrument that ensures patient's access to therapy with biological medicines, which may also assume one of the categories of restricted medical prescription[1] where prescription and/or use are restricted to certain specialised areas with closer monitoring of their safety profile. Overall, very severe adverse events can be induced by these medicines and the need for special monitoring is required throughout the treatment.[3]

Pharmacovigilance system and safety assurance

Regulatory framework

Pharmacovigilance systems have progressed from an approach oriented towards data collection, analysis and response to suspected adverse event reporting[3,4] to a new approach based on the promotion of risk management. Medicines segments with an increased risk profile associated with some degree of uncertainty and in need for additional monitoring were added.[5,6]

This progression has been underlined by European regulations (Table 1) and subsequent transposition (Table 2), asking for an adaptive dynamics of pharmacovigilance systems "complying with scientific and technical advances" and ensuring the safety of licensed medicines.[4]

Spontaneous suspected adverse event reporting is crucial in every pharmacovigilance system. Apart from the "harmful and involuntary effects of the licensed use of a medicine in normal dosage, (…) therapeutic errors and the use outside the terms of marketing authorisation, including misuse and abuse"[2] should also be considered. Adverse events include any untoward and unintended response to medicines.[13]

Prescription, dispensing and use

Mandatory electronic prescription, based on the international non-proprietary name (INN) of the active substance[14] and the inclusion of the brand name or the marketing authorisation holder are established by the regulatory framework (Table 3). Substitution of a medicine that has been prescribed by its brand name is not permitted under three situations which are reflected in legislaion[3] even though no specific reference is made regarding biological medicines.

As regards dispensing, these medicines are classified as subject to medical prescription or to restricted medical prescription and the latter are outpatient dispensed by the hospital pharmacy.[15] However, "procedures regarding the period of free supply of medicines, the information provided to the patient, the information record, the conditions regarding pharmacy dispensing or consultation are very different among hospitals, which may lead to differences regarding accessibility and the use of medicines."[16]

Prescription is restricted to designated centres where applicable[17] and these must provide for a quick response in case of any adverse event.[18] Designated centres for rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, polyarticular juvenile idiopathic arthritis and plaque psoriasis have been launched.[11]

Table 1 - Legal framework in the domain of pharmacovigilance

Legal document	Date	Scope	Transposition
Directive 2001/83/CE	6 Nov 01	Community code for medicinal products for human use	*Decreto-lei* no. 176/2006, 30 August
Directive 2004/27/CE	31 Mar 04	Amendment to Directive 2001/83/EC	*Decreto-lei* no. 176/2006, 30 August
Regulation 726/2004[7]	31 Mar 04	Community procedures for MA (marketing authorisation) and monitoring of medicinal products for human and veterinary use and implementation of European Medicines Agency	N/A
Regulation 1394/2007	13 Nov 07	Advanced therapy medicinal products	N/A
Regulation 1235/2010	15 Dec 10	Pharmacovigilance	N/A
Directive 2010/84/UE	15 Dec 10	Amendment to Directive 2001/83/EU	*Decreto-lei* no. 20/2013, 14 February, which is the seventh amendment to the *Decreto-Lei* no. 176/2006, 30 August
Directive 2011/62/UE	8 Jun 11	Amendment to the Directive 2001/83/UE aimed at preventing the introduction of counterfeit medicines into the legal supply chain	*Decreto-lei* no. 128/2013, 5 September
Commission Implementing Regulation 520/2012	19 Jun 12	Activities of pharmacovigilance defined by the Regulation (EC) 726/2004	N/A
Regulation 1027/2012[8]	25 Oct 12	Amendment to the Regulation 726/2004 on pharmacovigilance	N/A
Directive 2012/26/UE	27 Oct 12	Amendment to the Directive 2001/83/EC on pharmacovigilance	*Decreto-lei* no. 128/2013, 5 September
Commission Implementing Regulation 198/2013	7 Mar 13	Selection of an identification symbol for medicinal products for human use subject to additional monitoring	N/A
Regulation 357/2014[9]	3 Feb 14	Amendment to the Directive 2001/83/CE of the European Parliament and the Council and the Regulation (EU) 726/2004 of the European Parliament and the Council regarding the situations in which further post-authorisation efficacy data may be required	N/A
Regulation 658/2014[10]	15 May 14	Fees charged by the European Medicines Agency for the activities of pharmacovigilance regarding medicinal products for human use	N/A
Commission Delegated Regulation 2016/161	2 Oct 15	Rules for safety devices inserted within the packaging of medicinal products for human use	N/A

Source: Compilation made by the authors
N/A: Non applicable.

Prescription and dispensing of medicines aimed at the treatment of patients with Crohn's disease or ulcerative colitis only requires that prescription is made by gastroenterologists. These must be dispensed by the hospital pharmacy at the institution where the medication has been prescribed and the their use are subject to a monthly based monitoring.[19]

The orientations of the *Comissão Nacional de Farmácia e Terapêutica* established that active substances available as biosimilar medicines and less expensive medicines should be selected.[20] The use of medicines with the same brand name should also be guaranteed over the required

period of time in order to ensure traceability. Whenever alternating takes place, a precautionary principle must be applied. With the same objective, alternating between biosimilar medicines must comply with a minimum six-month period of time. Biological medicines are subject to additional monitoring due to their safety profile.[21,22]

The use of biologics in rheumatic diseases, psoriasis and inflammatory bowel diseases was regulated by the

Table 2 - National framework in the area of pharmacovigilance and other legislation applicable to biological and biosimilar medicines

Legal document	Date	Scope
Decreto-lei no. 176/2006	30 Aug 06	Medicinal products directive
Decreto-lei no. 20/2013	14 Feb 13	Seventh amendment to the *Decreto-lei* no. 176/2006 (Medicinal products directive)
Decreto-lei no. 128/2013	5 Sep 13	Transposition of Directive no. 2011/62/EU and no. 2012/26/EU regarding counterfeit medicines and pharmacovigilance; first amendment to the *Decreto-lei* no. 20/2013, which was the seventh amendment to the *Decreto-lei* no. 176/2006
Despacho no. 9767/2014	21 Jul 14	Definition of the conditions for prescription, dispensing and cost-sharing of medicines for treatment of patients with Crohn's disease or ulcerative colitis
Lei no. 51/2014[11]	25 Aug 14	Ninth amendment to the *Decreto-lei* no. 176/2006
Decreto-lei no. 52/2014	25 Aug 14	Definition of conditions required for access and cooperation regarding trans-frontier healthcare
Despacho no. 11042-F/2014	29 Aug 14	Definition of the model of medical prescription to be dispensed by a different member state
Portaria no. 48/2016	22 Mar 16	Definition of the conditions for dispensing and use of medicines aimed at the treatment of patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, polyarticular juvenile idiopathic arthritis and plaque psoriasis
Portaria no. 198/2016[12]	20 Jul 16	Amendment to the Appendix I of the *Portaria* no. 48/2016

Source: Compilation made by the authors.

Table 3 - Normative documents regarding prescription, dispensing and use of biological and biosimilar medicines in Portugal

Document	Issued by	Date	Scope
Circular Normativa no. 01/2015	SPMS	14 Jul 15	Methodology request of exemption for purchase according with the framework agreement of *SPMS*, *EPE*
Comissão Nacional de Farmácia e Terapêutica	INFARMED	Nov 15	Use of biological medicines in rheumatic diseases, psoriasis and inflammatory bowel diseases
Guideline 010/2014	DGS	23 Jul 14	Designated centres for the prescription of biological medicines
Guidelines regarding the prescription of medicines and health products	INFARMED ACSS	29 Oct 15	Prescription of medicines and health products
Guidelines regarding dispensing of medicines and health products	INFARMED ACSS	29 Oct 15	Dispensing of medicines and health products
Use of biological medicines in rheumatic diseases, psoriasis and inflammatory bowel diseases	INFARMED CNFT	Nov 15	Use of biological medicines in rheumatic diseases, psoriasis and inflammatory bowel diseases

Source: Compilation made by the authors.
ACSS: *Administração Central do Sistema de Saúde*; CNFT: *Comissão Nacional de Farmácia e Terapêutica*; DGS: *Direção Geral da Saúde*; INFARMED: *Autoridade Nacional do Medi*camento *e Produtos de Saúde*; SPMS: Serviços Partilhados do Ministério da Saúde.

Table 4 - Comparative analysis of the information within Portuguese adverse event reporting forms for patients and healthcare professionals

	Adverse event reporting form	
Medicine identification	Healthcare professionals	Patients
Full name of the medicine	–	X
Brand name	X	–
Pharmaceutical form	–	X
Dosage	X	X
Lot no.	X	X
Route of administration	X	X
Date of treatment onset	X	X
Date of treatment withdrawal	X	X
Medicine used for the first time	–	X
Daily dose	X	X
Therapeutic indication	X	X

Source: Suspected adverse event official Portuguese reporting form

Comissão Nacional de Farmácia e Terapêutica; clinical recommendations are provided in the guidelines (*Normas de Orientação Clínica*) of the *Direção Geral de Saúde* (DGS) upon scientific societies having been heard.[23]

Purchase of biological and biosimilar medicines by the institutions of the Portuguese healthcare system (SNS) is subject to the official determinations that binds to the dispositions within framework agreements. An exception system is expected whenever the continuity of therapy must be ensured and when interchangeability has not been proved.[24]

Information flow within the pharmacovigilance system

Information on safety of medicines is preferably collected through spontaneous suspected adverse event reporting made by healthcare professionals and by patients.[25] Specific forms are used by the INFARMED[26] (Table 4) and the information is collected and sent to the regional centres of pharmacovigilance and to the national authority – INFARMED and centralised by the European Medicines Agency through the EudraVigilance information system.

Traceability

The orientations of the *Comissão Nacional de Farmácia e Terapêutica* established that traceability of biological and biosimilar medicines must be ensured.[14] The *Direção Geral de Saúde* is required to keep record of every patient, in order to meet this objective.[11] Within a transition stage, until DGS system becomes operational, information is centralised by the INFARMED.[11]

As regards advanced therapy medicinal products, risk monitoring must contain a comprehensive connotation, with patient's total traceability, as well as regarding the product, basic and raw materials, including all those having had contact with cells or tissues that it may contain, for at least a 30-year period beyond the expiration date of the product.[27]

Impacts of trans-frontier healthcare

Trans-frontier patient mobility leads to healthcare extension to the perimeter of all member states.[28] This reality required for the definition of measures aimed at an easier mutual recognition of medical prescriptions and the model of medical prescription to be used in Portugal and to be dispensed in a different member state has been approved.[29] Therefore, prescription of biologics is complemented by trademark clarification.[30]

As regards financing with liability on the part of the affiliated member state, up to a maximum of three member states can be involved in the use of a medicine (different state members regarding medical prescription, dispensing and financing). Safety monitoring and therapy traceability assurance becomes even more complex within this tripartite framework.

Issues regarding counterfeit

The use of a Community code for medicinal products for human use has been established, aimed at preventing

from the entrance of counterfeit medicines into the legal market.[31] The Portuguese *Decreto-lei no. 128/2013* has established that, for biologics, knowing the brand name and the lot number is crucial and the pharmacovigilance system must be prepared to collect this information (article 167) through healthcare professionals (article 169) and the patients (article 172).[6]

This framework is on the way of a reconfiguration with the systematic use of safety devices within packaging of prescription medicines.[32] Advanced therapy medicinal products are not covered by this disposition.

DISCUSSION

Regulatory framework of the pharmacovigilance system has a cross-sectional application to every medicine, even though a progression towards adequacy to specific segments such as biological and biosimilar medicines can been observed.

Now is the time to look upstream and downstream of each regulatory intervention for the level of alignment with the remaining legal and operational dispositions. Three levels of discontinuity can be found: (1) in transposition from the European to the Portuguese legislation, (2) in the application of the national legislation into the development of normative documents and (3) in links between these and the operating systems.

Basic and initial framework of the activities of pharmacovigilance is minimalist[4] and no specificity as regards biologics is included. A subsequent legal document defined that biologics are not generic medicines[33] and the transposition of this document defined that adverse event reporting "includes the identification of these medicines by its name and lot number."[3]

The importance of pharmacovigilance for this segment of medicines is also described in the European legislation as "every appropriate measures should be taken in order to identify all biological medicines prescribed, distributed or sold within its territory and involved in reporting, considering the name of the medicine, (…) as well as the lot number"[2] and subsequently, in the transposition "the notifications of these suspicions regarding biological medicines that were prescribed, distributed or sold in Portugal, will identify these medicines by the name and the lot number." [7]

As regards the fight against the introduction of counterfeit medicines into the legal supply chain, no particular determination has been specified regarding biologics and biosimilars.[25] However, we may find in the eighth amendment to the *Decreto-lei no. 176/2006* that, regarding adverse events, "when reporting of these suspicions regarding biological medicines that were prescribed, distributed or sold in Portugal, these are identified by the name and the lot number."[6] In a different regulation, the need for the adoption of standard and urgent procedures regarding emergent safety issues is reinforced, even though no other specific reference has been made regarding biological medicines in any of the regulations.[5]

Therefore, considering the current Portuguese regulatory framework, six domains should be mentioned:

Prescription and outpatient dispensing of prescription medicines

No mention is made regarding any specific prescription and dispensing of biological medicines in the guidelines issued by the INFARMED and the ACSS.[12] As regards prescriptions, the use of the brand name is defined, apart from the use of the INN, even though no specific reference has been made regarding the use of this procedure when using biological medicines. This is an omission in regulation that must be corrected by a text revision. The reference to the lot number or to the marketing authorisation holder of biosimilar medicines is missing from the regulation, as well as the information on whether the prescription regards therapy onset or continuity.

Hospital-based prescription and dispensing of restricted prescription medicines

There is a regulatory framework involving the procedures and the instruments.[9,10] However, these are not adapted to therapy with biological and biosimilar medicines as recorded items do not allow for a complete characterisation and traceability of these medicines. There is a mandatory identification of the INN, dosage, pharmaceutical form, posology and therapy duration. However, any information on the brand name, lot number or reference to therapy onset or continuity is considered. In addition, the specific legal framework regarding the conditions for dispensing and use of biologics in anti-rheumatic therapy,[11] as well as in Crohn's disease and ulcerative colitis[13] does not include any of the abovementioned information, which would ensure a full knowledge on informative variables regarding the safety profile associated with these medicines.

Limitations to substitution of any prescribed biological medicine by brand name

Three situations have been defined in which substitution of any medicine prescribed by brand name is not possible,[3,8] to which we suggest the addition of a different paragraph based on the guidelines issued by the *Comissão Nacional de Farmácia e Terapêutica*.[14] According with this document, biosimilar medicines must be initially selected as the therapeutic option, even though in our opinion, whenever a prescription has been made by brand name, this should be kept. A precautionary principle is therefore reinforced.[14]

Adverse event reporting

Interchangeability must be taken into consideration by the reporting system as a possible cause for an adverse event, according with the guidelines of the *Comissão*

Nacional de Farmácia e Terapêutica. Therefore, the system must be prepared to incorporate any information associated with this domain, apart from the one focused on the medicine and which is already ensured by the *Decreto-lei nº 128/2013, 5 September.* The clinical experience in this domain gives a crucial contribution to the careful identification of potential adverse events and subsequent reporting to the pharmacovigilance system.

Committee for the analysis of the prescription of biological medicines

A Committee for the Analysis of the Prescription of Biological Medicines must be established[12] as it was defined by the guideline 010/2014 of the DGS. The analysis of prescription of biologics as well as patient's treatment regimens should be included among the functions of this committee, in order to ensure effectiveness, safety and adherence to therapy.

Addressing of an extended regulatory framework

Finally, reference should be made to chemically synthesized medicines with the same active substances as those biotechnologically obtained before. As these may be considered within the context of interchangeability and switching, these and other medicines – such as advanced therapy medicinal products - should be covered by the abovementioned dispositions.

CONCLUSION

Safety associated with the use of biological and biosimilar medicines has specific determinants not replicated in any other segment of the pharmaceutical market. Working in perfect tuning and synchrony within the different institutional levels of information is the main challenge to the system. Necessary steps should be taken aimed at the full adjustment and implementation of legal and operational frameworks regarding therapy with biological and biosimilar medicines, allowing for the promotion of internal consistency, in order to improve safety.

HUMAN AND ANIMAL PROTECTION

The authors declare that the followed procedures were according to regulations established by the Ethics and Clinical Research Committee and according to the Helsinki Declaration of the World Medical Association.

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