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Biosimilar drugs-reimbursement regulations.

Polish ISPOR chapter's Therapeutic Programs and Pharmaceutical Care (TPPC) task force report

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ABSTRACT

Objectives: Due to the increased number in biosimilar drugs getting marketing authorization, there is a question to be answered which reimbursement procedure should be followed

Methods: The TPPC task force has checked the approach to biosimilar drugs by WHO, at the EMA level and in a few countries worldwide. Among other aspects discussed, we concentrated on the production process of the reference (original) drugs and biosimilars and looked for differences. An internet search was performed checking the definitions as well as regulatory and reimbursement processes worldwide, with focus on the countries having HTA procedure in place.

Findings: It was found that due to specifics of biosimilars, detailed and comprehensive regulatory processes have been established centrally for EU states. No reimbursement guidelines have been identified. Due to lack of specific reimbursement guidelines TPPC agreed on a need to define a biosimilar drugs reimbursement process in Poland.

TPPC task force also agreed that due to central European registration process the definitions for biosimilar drug in Poland should be in line with the EMA guidelines.

The reimbursement process is different in each EU member state and it should be defined for these products on a country level. Probably, it also requires specific guidelines to be developed, especially in countries such as Polandwith "HTA dependent reimbursement process".

Conclusions: TPPC task force has only identified regulatory guidelines and its opinion is that in Poland, a detailed reimbursement process should be developed in the way it also includes the biosimilar drugs.

BACKGROUND AND OBJECTIVES

Since the European Union (EU) introduced the Directive 2004/27/EC biosimilar drugs started to be registered by European Medicines Agency (EMA)[1]. These drugs are similar to reference (original) biological drugs, which contain an active substance such as protein or protein complex and can be produced only by living cells. This group of drugs and the regulations related to registration/marketing authorisation create many discussions around the world. Especially the

immunogenicity is an issue which cannot be ignored. We do not always observe clinical effect with the antibodies formation. However, sometimes the clinical effects are significant and could be the cause of severe disease. Immunogenicity may impact efficacy, biodistribution and pharmacokinetics of the drug, which can cause toxicity and interfere with other therapeutic products. Hypersensitivity reactions, cross-neutralization of endogenous substances, or changes in physiological functions can also be a result of immunogenicity.

There are many drug-related factors which can have influence on the immunologic system, like manufacturing process, formulation, dosage, packaging process and storage conditions.

As the patients' safety is unquestionably of the biggest importance, the regulations implemented in the countries for registration/marketing authorisation and reimbursement should take it into consideration. Therefore, bearing in mind the interests of the patient, and in order to allocate public funds which are spent in the health sector in the best possible way, it would be reasonable if biosimilar drugs were subject to the same formalities as reference (original) drugs. Within the EU the drug registration/marketing authorisation process is unified with the central procedure, which is not the case in other countries across the world where the registration/marketing authorisation process is linked or followed by reimbursement process, which finally has an impact on drugs availability for patients. Due to more biosimilar drugs registrations expected in the future, there is a question to be answered regarding the reimbursement procedure to be followed.

Neither the provisions of 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 nor the Polish Act of September 6, 2001 Pharmaceutical Law does not provide a legal definition of biological or biosimilar product. Both legal regimes recognize, however, that the biological products which are similar to biological reference product (ie. biosimilar products) cannot be identified with generic products and, therefore, provide specific rules for the marketing authorization of biosimilar products. The TPPC task force searched for solutions in other countries, which could be implemented in Poland.

METHODOLOGY

The TPPC task force started discussions about the biosimilar drugs reimbursement pathways in 2011. The approach to biosimilar drugs worldwide with special focus on EU and at the EMA level was checked.

A review of current legal regulations concerning biosimilar drugs has been performed with special attention to definitions of biosimilar drug, regulatory processes implemented and reimbursement guidelines in place in different countries. There was no limitation towards the countries in scope.

Different databases have been reviewed to identify published regulations concerning biosimilar drugs across the whole world. Special search focus was on reimbursement regulations and on guidelines issued by worldwide known and experienced Health Technology Assessment (HTA) Agencies. The Polish HTA, when preparing the verification analysis related to the assessed product, checks the reimbursement guidelines issued by National Institute for Health and Clinical Excellence in UK (NICE), in Scotland by the Scottish Medicines Consortium (SMC), by Haute Autorite de la Sante in France (HAS), in Australia by Pharmaceutical Benefits Advisory Committee (PBAC), and in Canada by the Canadian Agency for Drugs and Technologies in Health (CADTH)[2].

The search done by TPPC focused on the following words: "biosimilars", "biosimilar drug definition", "guidelines", "HTA", "reimbursement", "reimbursement guidelines" and it was conducted using Internet.

THE TPPC TASK FORCE STARTED DISCUSSIONS ABOUT THE BIOSIMILAR DRUGS REIMBURSEMENT PATHWAYS IN 2011. THE APPROACH TO BIOSIMILAR DRUGS WORLDWIDE WITH SPECIAL FOCUS ON EU AND AT THE EMA LEVEL WAS CHECKED.

The identified definitions and regulations have been presented at the TPPC task force meetings and discussed by team members in terms of suitability for adaptation to the Polish health care system.

FINDINGS

Among other aspects discussed by the task force, we concentrated on the production process of the reference (original) biologic drugs and a biosimilar drug looking for differences. Finally an agreement was reached that following EMA regulations there is a need to define what a biosimilar drug is in the Polish legal system. The TPPC task force agreed on the following definition:

Biosimilar drug is a drug produced using biotechnological methodology and it is similar in terms of medicinal product design, pharmacological and pharmacokinetic properties, safety and efficacy, but not identical to the original registered and authorized reference biological medicinal product.

This definition was presented to the Board at the Polish ISPOR Chapter meeting in December 2011 as the one proposed to be included in the future legal acts regarding reimbursement and HTA.

Regarding legal regulations on biologic drugs legislation including biosimilar drugs search, it was found that the regulations started to be prepared and implemented in those countries where the biosimilar drugs are already in the market or are expected in a short term.

In 2012 EMA issued a draft revised 'overarching' guideline on similar biological (biosimilar) medicinal products for consultation. In addition, EMA have issued and continue to update product specific biosimilar guidelines which are available on the EMA website[3].

Among other information available on EMA website the following definition on biosimilars can be found: "a similar biological or ‚biosimilar' medicine is a biological medicine that is similar to another biological medicine that has already been authorised for use", "Biological medicines are medicines that are made by or derived from a biological source, such as a bacterium or yeast. They can consist of relatively small molecules such as human insulin or erythropoietin, or complex molecules such as monoclonal antibodies[4].

So far, EMA have assessed 15 applications on biosimilars submitted by different com-

panies, 12 out of 15 have been authorized by EMA for use in the EU (including one with patient safety warning), for 1 biosimilar EMA has recommended the refusal of marketing authorization and for 2 biosimilar drugs the marketing authorisations have been withdrawn at the request of the marketing-authorisation holders (companies)[5].

Apart from the detailed guidelines taking into account transparency issues for the public, EMA publishes general information on biosimilars, including requirements for authorization of biosimilar medicines, indicating that the company needs to carry out studiesto show that the medicine is similar to the reference medicine, does not have any meaningful differences from the reference medicine in terms of quality, safety or efficacy[4]. EMA, in the last Directive regarding pharmacovigilance and amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, considers safety monitoring of biosimilar drugs as a priority. It states that some medicinal products are authorised subject to additional monitoring. This includes all medicinal products with a new active substance and biological medicinal products, including biosimilars, which are priorities for pharmacovigilance[6].

For transparency reasons, in September 2012, EMA published a brief document titled "Questions and answers on biosimilar medicines (similar biological medicinal products)"[7]. EMA published first adopted guidelines on similar biological medicinal products in September 2005 (effective since October 2005) as the result of Committee for Medicinal Products for Human Use (CHMP) discussion which took place in June-November 2004[8].

The approach by the World Health Organization (WHO) is that biosimilar medicines are biotherapeutic products that are similar in terms of quality, safety and efficacy to the reference product already licensed. WHO provides globally accepted norms and standards for the evaluation of biosimilar products. Written standards established through the Expert Committee on Biological Standardization (ECBS) serve as a basis for setting national requirements for production, quality control and overall regulation of biological medicines. In addition, International Standards for measurement are essential tools for the establishment of potential for biological medicines worldwide. Therefore, WHO has developed guidelines for the assessment of biosimilar products (SBPs)[9]. The intention of this document is to provide globally acceptable principles for licensing biotherapeutic products that are claimed to be similar to biotherapeutic products of assured quality, safety, and efficacy that have been licensed based on a full licensing dossier. On the basis of proven similarity, the licensing of SBPs will rely, in part, on non-clinical and clinical data generated with an already licensed reference biotherapeutic product (RBP). This guideline can be adopted as a whole, or partially, by national registration authorities worldwide or used as a basis for establishing national regulatory frameworks for licensure of these products.

WHO guidelines specify the key principles of licensing SBPs that indicate the need to demonstrate comparability to the reference product in both preclinical studies and clinical trials. Full documentation on the quality of both the drug substance and the drug product is always required to meet the standards required by the national regulatory authorities in relation to innovative products[9].

In the United States (US) the Food and Drug Administration Agency (FDA) defines that a biosimilar is a biological product that is highly similar to a U.S.-licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product[10].

The Association of British Pharmaceutical Industry (ABPI) working on the biosimilar topic recommended that biosimilar medicines should be subject to full Health Technology Assessment processes in the UK as for other medicines in order that they can be appropriately assessed for clinical and cost effectiveness using the appropriate evidence base. It should be stated clearly in the main section of the HTA guidance that is issued that the medicine appraised is a biosimilar[11].

ABPI also recommends that biosimilar products should be recorded on UK PharmaScan by companies as soon as they enter Phase III clinical trials or within three years of their expected launch date so they can be reported upon by the NHS horizon scanning agencies for HTA topic selection purposes[11].

The Scottish Medicines Consortium (SMC) and All Wales Medicine Strategy Group (AWMSG) (where appropriate) should routinely appraise biosimilar medicines and the NICE topic selection process should be used to identify those biosimilars which should be subject to NICE appraisal[11].

In Australia Pharmaceutical Benefit Advisory Committee (PBAC) an independent statutory advisory body to Minister of Health in its current guidelines for HTA (2008 version of the PBAC Guidelines) plan as next step to consider further guidance in relation to other technical policy issues and, among others, the biosimilars are in scope[12].

Japan's Ministry of Health, Labour and Welfare (MHLW) has issued guidance on biosimilars, which sets out the policies regarding requests on development and regulatory approval application for biosimilars in Japan, according to a report by Pharma Japan[13]. The definition is as follows: „Biosimilars are drugs which are equivalent and homogeneous to original biopharmaceuticals in terms of quality, efficacy and safety and which are developed by manufacturers different from those of the original biopharmaceuticals".

WHO guidelines were used as a reference and basis to create local guidelines in many countries. The organization makes the information about the adapted and implemented guidelines available on their website.

According to the published information the biosimilar drug is defined and regulatory guidelines are available in the following Latin American countries[14].

The President of Mexican United States in 2011 issued a Decree that amends and adds various provisions to the regulation of health supplies, defining SBP as non-innovative biotechnological drug that proves to be bio-comparable in terms of safety, quality, and effectiveness, based on the specific tests established for this purpose by the law.

In Cuba in 2011 the Ministry of Health published the Resolution number 56/2011 specifying the requisites for registration of known biological products, and according to that resolution the SBP is a biological product produced by multiple manufacturers, in which the active substance is comparable in terms of quality, safety, and efficacy profiles to the active substance of an already licensed RBP in Cuba or in other countries. The dosage form, the potency, and indications should be the same as those of the RBP.

In Guatemala, biosimilar drug is defined as biologic/biotechnological medication that has demonstrated, by an exercise of biosimilarity and biocomparability, that is similar or comparable in terms of quality, safety, efficacy, and immunogenicity to the reference medication (Technical standard 67-2010: Sanitary reference registry of biological and biotechnological products/Ministry of public health and social assistance, 2010).

Costa Rica defines SBP as biological

medication that has been demonstrated by the exercise of biosimilarity to be similar in terms of quality, safety, and efficacy to the reference biological medication (RTCR 440: 2010 Regulation on the inscription and control of biological medications/ Presidency of the Republic – Ministry of Health).

Regulatory guidelines related to biosimilar drugs were also identified in India, Saudi Arabia, Turkey, Iran, Pakistan and Korea.

In India in 2012 the "Guidelines on Similar Biologics" have been published. They were prepared by Central Drugs Standard Control Organization (CDSCO) and the Department of Biotechnology (DBT) lay down the regulatory pathway for a similar biologic claiming to be similar to an already authorized reference biologic[15].

JAPAN'S MINISTRY OF HEALTH, LABOUR AND WELFARE (MHLW) HAS ISSUED GUIDANCE ON BIOSIMILARS, WHICH SETS OUT THE POLICIES REGARDING REQUESTS ON DEVELOPMENT AND REGULATORY APPROVAL APPLICATION FOR BIOSIMILARS IN JAPAN, ACCORDING TO A REPORT BY PHARMA JAPAN

The guidelines address the regulatory pathway regarding manufacturing process and quality aspects for similar biologics. These guidelines also address the pre-market regulatory requirements including comparability exercise for quality, preclinical and clinical studies and post market regulatory requirements for similar biologics[15].

The Drug Sector of the Saudi Food and Drug Authority (SFDA) as an organization that is concerned about availability of medicines and safety of patients, in December 2010 issued the guidelines related to biosimilar drugs registration process in Saudi Arabia[16]. The content of this document was assembled through extensive search and research of the European Medicines Agency (EMEA) Guidelines, the International Conference on Harmonization (ICH) Guidelines and other resources including published, peer reviewed articles. The guidelines should be revisited biannually for evaluation, improvement, revision, and amendment. Just as for conventional chemical products, the prerequisites for marketing authorization of a biosimilar are proof of quality, safety, and efficacy. These three issues must be clearly addressed when assessing comparability between a biosimilar and the reference medicinal product.

In Turkey the first guidelines for registration of biosimilar drugs were published in 2008, since that time some changes have been introduced[17]. The document introduced the concept of biosimilar medicinal products and guidelines for application. Reference documents for similarity statements and definitions were EMEA/CHMP guidelines.

The parliament in Pakistan approved mandate of the Drug Regulatory Authority of Pakistan (DRAP), but also defined a separate registration pathway for Biologics and guidelines for Biosimilars (in line with WHO Guidelines)[18].

In Korea biosimilar product is regulated under the same regulation as biological products. The difference from new biological product is that biosimilar product requires full comparability data with reference product. Korean guideline for biosimilar products was developed in line with the WHO's guidelines and most of the recommendations were based on similar principle. The difference is in relation to the clinical evaluation required to demonstrate similarity[19].

DISCUSSION

Poland being part of EU follows the EMA regulations in relation to the regulatory process. EMA is working on the best approach to biosimilar drugs implementation in Europe but the focus is on the regulatory process taking into consideration the differences towards the reference (original) biological drugs and safety issues. However, drug registration/marketing authorisation is not equal to access to treatment. Many European countries have specific reimbursement procedures or guidelines in place and some of them take into account the economic arguments in the decision-making process. In those countries there are special agencies or dedicated governmental bodies estab-

lished to assess the new health technology impact on the healthcare system, clinical and economic value of the new technology and its safety. As an example we can consider the impact of NICE on the final decisions to finance a new product in UK or the Polish HTA agency (AHTAPOL) influence in Poland.

The TPPC task force, as part of the Polish Pharmacoeconomical Society, is interested in the current reimbursement regulations and is looking for the future trends within the Drug dedicated Programs in Poland which have identified biosimilars entry into the Programs as a potential field for further development and discussion. Firstly the biosimilar drug definition was discussed as the starting point for further discussion. There is no doubt that Poland being a member of EU should follow EMA regulations and the definition proposed by Polish TPPC task force was in line with the one proposed by EMA.

Concentrating the efforts on reimbursement guidelines it was expected that during the search a reimbursement specific guidelines or HTA guidelines which would include an approach to biosimilar drugs would be identified. This has not happened. In our opinion it does not mean that there is no need for such guidelines. The example of PBAC in Australia, planning inclusion of biosimilar drugs in the next HTA guidelines edition confirmed the TPPC task forces opinion that a similar process is needed in Poland. Members of TPPC task force discussed it and agreed on the need to include, the definition of biosimilar drugs in the existing guidelines for Poland and also to define the requirements to be fulfilled for reimbursement.

CONCLUSIONS

Having EMA, WHO and FDA guidelines in place is not enough. Local regulations and legal acts should address multiple areas, going beyond the regulatory approval process. Due to only regulatory guidelines being identified, the TPPC task force's opinion is that in Poland, a country which has HTA regulations in place, a detailed reimbursement process should be developed including the biosimilar drugs' presence. It should not be solely limited to the cost – effectiveness of the new technologies and the impact on payer's budget but also the evaluation of the efficacy and safety in comparison to the standard therapy used should be considered. ■

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REFERENCES:

1. Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004. [cited 29 November 2012]. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0034:0057:EN:PDF
2. Analizy weryfikacyjne Agencji Oceny Technologii Medycznych 2012. [cited 28 November 2012]. Available from: http://www.aotm.gov.pl/bip/index.php/zlecenia-mz-2012
3. European Medicines Agency: Lists the European Medicines Agency's scientific guidance documents on biosimilar medicines. [cited 29 November 2012]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&mid=WC0b01ac058002958c
4. European Medicines Agency: Biosimilar medicines. [cited 6 January 2013]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000318.jsp&mid=WC0b01ac0580281bf0
5. European Medicines Agency: European public assessment reports. [cited data 6 January 2013]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByAuthType&alreadyLoaded=true&isNewQuery=true&status=Authorised&status=Withdrawn&status=Suspended&status=Refused&keyword=Enter+keywords&searchType=name&taxonomyPath=&treeNumber=&searchGenericType=biosimilars&genericsKeywordSearch=Submit
6. Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use; Official Journal of the European Union L 348; 31.12.2010
7. European Medicines Agency: Questions and answers on biosimilar medicines (similar biological medicinal products), EMA/837805/2011, 27 September 2012. [cited 6 January 2013]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf
8. European Medicines Agency: Guideline On Similar Biological Medicinal Products, CHMP/437/04 London, 30 October 2005. [cited 6 January 2013]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf
9. World Health Organization: Guidelines on evaluation of similar biotherapeutic products (SBPs) 2009. [cited 28 November 2012]. Available from: http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf
10. Food and Drug Administration: Information for Healthcare Professionals (Biosimilars). [cited 6 January 2013]. Available from: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241719.htm
11. Association of British Pharmaceutical Industry UK: ABPI position on biosimilar medicines. [cited 29 November 2012]. Available from: http://www.abpi.org.uk/our-work/library/industry/Documents/ABPI%20biosimilars%20position%20paper.pdf
12. Australian Government Department of Health and Ageing: Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3) December 2008, section 2.4, p.15. [cited 29 November 2012]. Available from: http://www.pbs.gov.au/info/industry/listing/elements/pbac-guidelines/a-part-1/section-2
13. Japan's Ministry of Health, Labour and Welfare: Issues Guidelines on Biosimilars Development and Regulatory Applications. [cited 8 December 2012]. Available from: http://www.ihs.com/products/global-insight/industry-economic-report.asp
14. Desanvicente-Celis Z., Caro-Moreno J., Enciso-Zuluaga M., Anaya J.M.: Similar biotherapeutic products in Latin America. Regulation and opportunities for patients with autoimmune diseases. Biosimilars, 2013, 3:1-17. [cited 8 January 2012]. Available from: http://www.dovepress.com/similar-biotherapeutic-products-in-latin-america-regulation-and-opport-peer-reviewed-article-BS
15. Government of India, Ministry of Science and Technology, Ministry of Health and Family Welfare: Guidelines in Similar Biologics: regulatory requirements for marketing authorization in India 2012. [cited 29 November 2012]. Available from: http://dbtbiosafety.nic.in/Files/CDSCO-DBTSimilarBiologicsfinal.pdf
16. Saudi Food and Drug Authority: Biosimilar Guidelines Saudi Arabia. [cited 29 November 2012]. Available from: http://www.sfda.gov.sa/NR/rdonlyres/CB28C6AF-79CD-4412-8801-35AEDEED0183/0/Guidelinesonbiosimilars_v11.pdf
17. Turkish Pharmaceuticals and Pharmacy General Directorate: Biosimilar Medicinal Products Guide. [cited 29 November 2012]. Available from: http://www.iegm.gov.tr/Folders/TheLaws/BiobenzerKilavuzu,07.08.2008,Eng.4621062.pdf
18. Drug Regulatory Authority of Pakistan: Bill to Provide for the Establishment of Drug Regulatory Authority of Pakistan 2012, Available from: http://www.senate.gov.pk/Legis%20Br/bill/drap2012.pdf, access 28 November 2012. [cited 19 February 2013]. Available from: http://apps.who.int/medicinedocs/en/m/abstract/Js19950en
19. Soo Kyung Suh, Younjoo Park: Regulatory guideline for biosimilar products in Korea, Biologicals 39 (2011); 336-338