I. INTRODUCTION

This document aims to present the position of the pharmaceutical companies which produce innovative biological medicines (member companies of Local American Working Group: Abbvie, Amgen, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Glaxo Smith Kline, Janssen of Johnson & Johnson, Merck Sharp & Dohme, Novartis, Pfizer together with Roche Romania) and to outline the distinctiveness of biological products, in order to improve aspects regarding the awareness and the regulation of this category of medicines.

According to the latest data [1], the use of biotechnology in the development process of new therapies is increasing and it is estimated that, at global level, the biological medicines will become the mostly used medical products over the following years.

The application of biological matter in medicine has a long history, with many attempts from scientists to use microorganisms in order to create different products, developing in this way the biotechnology. The term biotechnology was used for the first time in 1919 by the engineer of Hungarian origin Karl Ereky [2], his vision being more amazing if we take into account that the biotechnology instruments had not yet been discovered. The beginning of 1980 accounted for pioneering in biotechnology industry, few companies acknowledging and investing in the medical potential in this sector which gained ground rapidly. Nowadays, biotechnology revolutionizes the diagnosis of diseases with genetic predisposition, whereas the medical innovation achieved by biopharmaceutical engineering helps to treat the most chronic diseases (cancer, diabetes, cardiovascular, renal, dermatologic disease, Alzheimer disease, Parkinson disease, hepatitis etc).

The European Medicines Agency [3] defines biological products as medicines that include one or more active substances produced or obtained from a biological source. The active substances in the biological medicines are in a higher percentage and more complex than those from non-biological medicines and the living organisms are the only ones that can reproduce this complexity. Some biological medicines are reproductions of various substances that are already present in the human body, such as proteins, insulin, the growth hormone and erythropoietin. Others are obtained by processing the human blood, organs and animal tissues, resulting in vaccines and recombinant DNA. At the global level, the lives of over 350 million patients have been improved due to the treatments with biological medicines [4].

Some of the innovative biological products (e.g.: proteins, monoclonal antibodies) have already lost their patent or their data exclusivity, others will lose them in the near future. As a result, biological products that are considered to be similar with the originator products – called "biosimilars" – have started to be authorized in accordance with the European legislation.

The companies producing innovative biological medicines, members of LAWG, together with Roche Romania, are companies that devote their efforts to respect high moral standards and to esteem the physicians’ right to prescribe biological products, as well as supporting the welfare of patients who rely on the quality, safety and efficacy of the medicines. We support the development of the regulatory framework for the approval and correct use of biological medicines, in the benefit of the patients, and we want to engage actively in a constructive dialogue with all the interested parties. This entire framework will provide a constant and high level of public health protection, for the use of innovative biological products, original, as well as for biosimilar medicines.

II. CHARACTERISTICS OF BIOLOGICAL MEDICINES

The biological medicines are developed from living cells or living organisms, through medical bioengineering, unlike traditional medicines which are obtained through chemical synthesis. There are several reasons for which their production is more complex, such as the raw material used, the heterogeneous structure, the more complex production process, additional quality controls, as well as sensitivity to storage and operation.
The biological medicines, including the ones obtained only from human tissue, are immunogenic, having the capacity to induce an immune answer to the treated patient. Immunogenicity is a dynamic factor that must be taken into account in the prescription and administration of biological medicines. Immunogenicity testing is a critical component in product development. Without the assessment on human subjects, it is not possible to predict the degree of immune response and its consequences. The understanding of the biological therapies’ immunogenicity and the way it can be managed is useful not only for the optimization of the treatment strategy, but also for the design of predictive models of answer and for the targeted treatments.

A specific case of biological products is represented by biosimilar medicines, developed in order to be similar to the existing biological medicine (“biological medicine of reference”) [6], but not identical. Moreover, biosimilars are not the same with generic medicines, that have simpler chemical structures and are considered identical with their medicines of chemical synthesis of reference. The European Medicines Agency (EMA) evaluates biosimilar medicines in order to be authorized. Although they rely on a similar active substance as the one from reference medicines, EMA doesn’t make recommendations in terms of the interchangeable use of the biosimilar medicine with the medicine of reference, urging for a consultation with the physician or the pharmacist in this respect, for each clinical case in particular. There can be differences between the biosimilar and the biologic of reference, as a result of their complex nature and of the production methods. In order to be approved, the biosimilar needs to prove that its variability and other differences from its medicine of reference don’t affect safety or efficacy of treatment.

Comparability and similarity – close concepts, but based on different acknowledgements

Proving that a certain biotherapeutic product is (bio)similar with a product of reference, developed by another producer, requires numerous and complex data, in contrast to that necessary for the assessment of comparability for a product before and after a change has been made to the medicine, in the sense of improving the fabrication process. A producer who modifies a well-defined and approved fabrication process has extensive knowledge and information about the product and the already existent process, including on well-defined control mechanisms, on acceptability parameters as well as a vast data base about the clinical experience of product development.

This will facilitate the achievement of an analytical comparability, more specifically, the demonstration that the pre- and post-modification of the fabrication process are highly similar in terms of safety and efficacy. Unlike the former situation, it is quite possible that the producer of the biosimilar product can use a different fabrication process (namely cellular line, materials, equipments, processes, control mechanisms and different acceptability parameters) compared to that of the product of reference, not having direct knowledge about the fabrication process of this one. Due to the structural complexity of biotherapeutic products, differences are expected between the biosimilar products and the product of reference. In the absence of clinical experience, the potential impact of these differences, from the point of view of safety and efficacy, can’t be predicted based only on the analytical assessment. For this reason, multiple data is necessary for the biosimilar products and it should always conduct comparative clinical studies before granting the marketing authorization.

Importance of comparability for biosimilars [7]

„Data requirements for biosimilar medicinal products are higher than when assessing a process change for the same product. It should be noted that a comparability exercise is also required for originator biological medicinal products when changes to the manufacturing process are made. Indeed, such changes are frequently introduced throughout a product’s lifecycle (e.g., to improve the quality or to increase the yield of the product). As a consequence, the quality profile of the biological product may evolve over its life cycle but would still be considered as comparable to the product before changes were made as long as relevant impact on safety and efficacy has been excluded with sufficient confidence. The scientific principles underlying the comparability exercise required for changes in the manufacturing process of a given biological product and for the development of a biosimilar product are the same. Even so, data requirements for the latter are higher and, at least in the EU, always include clinical studies because, due to the completely independent manufacturing processes, some differences between the biosimilar and the reference product can be expected, and the potential impact of these differences on safety and efficacy cannot be predicted from analytical assessment alone.”

Martina Weise – representative of Biosimilar Medicinal Products Working Party (BMWP) at EMA
The Directive 83/2001 concerning the establishment of a Community code related to the medicines of human use;

The European Commission Regulation no. 726/2004 of establishment of the community procedures related to the authorization and monitoring of the medicines of human and veterinary use and of setting up a European Medicines Agency;

Many guides drawn up by the regulatory authorities.

EMA considered necessary to develop such special guides for biosimilar products, which are seen as a distinctive category, but not for the biological medicines of reference, based on taking into account the different character of the two types of medicines. The biosimilar product is not a generic of the biological product of reference and it requires separate monitoring and different approach. We also state the fact that even in the Romanian National Catalogue of the prices of medicines for human use authorized to be introduced on the market (CANAMED), biosimilars are a distinctive category compared to the innovative and generic medicines (the existing categories are: innovative, generics and biosimilars).

Starting from 2005, the European Union has a common regulatory system where the biosimilar medicines are approved at centralized level by EMA. At national level, the regulations in terms of the requirements for biosimilars medicines are the same as the European ones.

### Prescription

Although this is a topic attributed to the member states, the European Commission has considered necessary to intervene in case of medical prescriptions issued in another member state, different than the one where the medical prescriptions are issued, thus:

- The Directive 2012/52/EC to establish some measures in order to facilitate the acknowledgement of medical prescriptions issued in another member state – adopts a non-exhaustive list of the elements that must be included in these prescriptions and that should facilitate the correct identification of the medicines. Under the Appendix of this Directive, the commercial name of the medicine is mandatory in case the product prescribed is a biological medicine.

**National legislation requires for the prescription of biological medicines to be made based on the brand name, starting from the specific character of each product. The regulations in this respect are:**

- Article 145 of HG 400/2014 related to the approval of CO-CA.
- Article 5 para. 5 of OMS/CNAS/619/300/2014 related to the approval of Standards.
- Article 23 of HG 124/2013 related to the approval of the National Health Programs.
- Article 30 OPCNAS 190/2013.
- OMS 1301/500/2008 for the implementation of therapeutic protocols related to the prescription of medicines – there are in certain therapeutic areas specific regulations for biological medicines.

### Automatic substitution

In the context of assessments for authorization, EMA doesn’t make recommendations related to the interchangeable use of the biosimilar medicine with the medicine of reference. Although EMA directed the problem of the substitution at the pharmacies’ level up to the member states, currently none of the EU member states allow automated substitution (in the pharmacy) for the biosimilar products [10]. In order to improve the traceability of the biological products, the use of the brand name is mandatory in the medical prescription and, according to the Romanian legislation, should be clearly mentioned (recorded) in the patient records as well.

### Specific elements to the authorization of biosimilars [9]

- The standard approach used in case of generic medicines in order to prove similarity is not enough in case of biosimilar medicines, being necessary a comprehensive comparability exercise (in particular from the perspective of changing the fabrication process).
- The comparison of the data related to the safety and efficacy of a biosimilar with the product of reference must be proved or otherwise justified with data.
- If biosimilarity was proved in an indication, the extrapolation to other indications of the product of reference might be acceptable with an appropriate scientific justification.
- Clinical data are required aimed to confirm the comparability of the clinical performances of biosimilar and of the product of reference.
- If the comparability exercise of biosimilar shows the existence of relevant differences compared to the product of reference, which makes less possible the establishment of biosimilarity, an independent development process of the product must be taken into account in order to get an authorization of original product.

### The regulations evolution at European level of the guides for biosimilar products [8]

<table>
<thead>
<tr>
<th>The EMA guides:</th>
<th>Published on:</th>
<th>In force from:</th>
</tr>
</thead>
<tbody>
<tr>
<td>The guide related to the biological similar products that include proteins derived from biotechnology, as an active substance: non-clinical and clinical aspects (EMEA/CHMP/BWP/42832/2005 Rev1)</td>
<td>January 2015</td>
<td>July 2015</td>
</tr>
<tr>
<td>The guide related to the similar biological medicines (CHMP/437/04 Rev 1)</td>
<td>October 2014</td>
<td>April 30, 2015</td>
</tr>
<tr>
<td>The guide related to the similar biological medicines that include proteins derived from biotechnology as active substance – quality problems (EMA / CHMP / PPV / 247713/2012)</td>
<td>June 2014</td>
<td>December 1, 2014</td>
</tr>
<tr>
<td>The guide related to the similar biological medicines that include proteins derived from biotechnology – active substance – non-clinical and clinical aspects (EMA/CHMP/BWP/42832/2005)</td>
<td>February 2006</td>
<td>June 1, 2006</td>
</tr>
<tr>
<td>The guide related to the similar biological medicines that include proteins derived from biotechnology as active substance – quality problems (EMA/CHMP/BWP/49348/2005)</td>
<td>February 2006</td>
<td>June 1, 2006</td>
</tr>
<tr>
<td>The guide related to the similar biological medicines (CHMP/437/04)</td>
<td>September 2005</td>
<td>October 2005</td>
</tr>
</tbody>
</table>
To support the above mentioned principle, we refer to the new proposal of Government Decision on the approval of national health programs for the years 2015 and 2016 (Art. 10, h) which stipulates that an innovative drug cannot be replaced by a biosimilar medicine without the recommendation of the physician specialist, proposal that comes precisely to regulate this aspect.

The repeated change of the patients’ therapy with different biological medicines can lead to the appearance of additional risks. In this context, biosimilars’ authorization and commercialization should not suppose automated substitution of the product of reference and/or interchangeability of the product without the approval of the physician.

**Price**

The biological medicines comply with the same price regulations as the synthesis medicines. There is one difference, namely the regulation of the Article 3, letter l) of The Minister of Health Order no. 75/2009 for the approval of Norms related to the calculation method of the prices for medicines of human use. It states that the price of a biosimilar medicine can be up to 80% of the price of the biological product of reference (compared to maximum 65% in case of generic medicines).

**Pharmacovigilance**

The complexity of biological therapies claims for permanent monitoring of the patient from the perspective of risks and his safety. From the aspect of the pharmacovigilance process (as it is regulated by Article 102(e) of the Directive 2001/83/EC), all measures must be taken for clear identification of any biological product that can cause possible adverse reactions, by having a specific mention to the commercial name and to the lot number to which the respective medicine belongs [11].

In the case of biosimilars, permanent monitoring of possible adverse effects is compulsory, even if the original medicine proved its safety in use, given the variations that might appear in the production process. This additional monitoring is not applicable in case of generic medicines [12].

**IV. BIOLOGICAL MEDICINES IN ROMANIA**

In Romania there is still a low degree of medical biotechnologies usage compared to other countries within the EU or even globally, this leading to a lower level of information about the implications and the specificities of such therapies. Most of the information available about biological medicines refers to the comparison of the original biological medicines with the biosimilars, whereas less information can be found related to the specificities of biological medicines and aspects related to the safety of patients or the provision of their traceability.

Taking into account the fact that there has been no analysis up until now in Romania related to the public degree of knowledge about biological medicines or to the general perception of this topic, in 2014 the association Local American Working Group together with Roche Romania took the initiative of an assessment about the acknowledgements of using biological medicines. The assessment that relies on the opinions from representatives of authorities and interested parties, highlighted the fact that further detailed information is necessary (in case of those who use or regulate them) on the specificities of biological medicines.

Considering the above-mentioned context, in association with the opinions resulting from consultations with interested parties, we consider appropriate the effort to increase the awareness of the decision factors and interested parties about the biological treatments and their specificities, with the purpose of a higher access of the patients to such treatments and their usage with maximum safety.

**V. RECOMMENDATIONS FOR ACTION**

Biological medicines represent an essential discovery for the health care of the patients, with hard-to-reach therapeutic benefits, if not impossible, by the conventional medicines. Therefore, taking into account their particularities and complexity, we consider important the following recommendations for action:

1. **Raising awareness on biological medicines**
   - Taking into account the technological processes advance at the global level for the development of these therapies and of their renown benefits, we consider that the topic of biological medicines must become part of the public agenda, in the sense of informing about the originality and the impact of this class of medicines in order to reach the level of the decision factors, of the medical structures, but also of the patients.
   - Confusion between biosimilar medicines and the biological medicines of reference, has been observed, due to the fact that they have the same international trade name (INN). It is important to state that although the two types of medicines are based on similar active substances, the structure of cells used in the production process is different. As a result, biosimilars are not identical copies of the reference product.

   Also, the biosimilar medicines are not generic medicines. Generics (small molecules) are usually produced from chemical synthesis, while most biological drugs are produced in living systems, such as microorganisms or animal cells purified through a complex manufacturing process. In case of generic medicines, the studies characterize these molecules as being identical with the original one (the active substance is always the same), the variation in the clinical effects and the secondary effects are minimum, and the regulations accept equivalence. In case of biosimilar medicines, the active substance can have variations and the structure can differ from the biological of reference, as well as some variations can occur in the production process, depending on the body used, and for this reason regulations do not accept equivalence and additional clinical data is required.
2. The prescription of biological medicines should be made henceforth on brand name
   - The biological medicines are prescribed on their brand name (not on INN), according to the current national legislation and to the cross-border directive, the main reason being the patients’ safety and the provision of their traceability. We consider this measure beneficial because it gives the physician the possibility to decide on the most appropriate treatment for the patient and not otherwise (the patient to choose), as well as a better traceability in case of these medicines.

3. The automatic substitution in pharmacy is not recommended, the biological medicines being subject to substitution only under direct observation and with the physician’s consent
   - Due to reasons related to patients’ safety, the biological medicines cannot be changed at the level of the pharmacy (automatic substitution), but only under the prescription of the attending physician. We believe that the current prescription procedure for the medicines (on brand name) by physicians is correct, based on their expertise and the scientific motivation, in particular for the patients’ safety and the biological medicines’ traceability provision.
   - Automatic substitution could interfere with the obligations of producing companies after obtaining marketing authorization (Post Marketing Commitments), which are assumed obligations for the correct and complete implementation of the Risk Management Plan required by regulators.
   - Colectarea datelor din practica clinică („real-world data”) este importantă pentru toate indicațiile medicamentelor biologice și biosimilare, mai ales pentru indicațiile aprobate prin extrapolare. De importanță majoră este asigurarea unor activități de fază IV robuste, pentru a putea colecta date clare și transparente care să conferme profilul de eficacitate și siguranță al acestor medicamente.
   - Data collection in clinical practice (“real-world data”) is important for all indications and biosimilar biological medicinal products, especially for those approved through extrapolation. It is of major importance to ensure robust Phase IV activities in order to collect clear and transparent data able to confirm the efficacy and safety profile of these medicines.

4. The change of the treatment by the physician requires the existence of clear guides to state the conditions for the transfer
   - Taking into account the risks for patients in case of an unjustified change of the treatment, we support the introduction of guides stipulating the conditions under which the attending physician can opt for the change of medicine at a patient that is under treatment with a biological medicine (innovative or similar).
   - Therefore, we encourage the correct information of the patients by the physician related to the changes brought to the existing treatment.
   - We argue that the decision to choose the treatment should not be based on cost considerations, but to rely on the clinical justification and on the therapeutic effects that are beneficial for every patient.

5. Access of biosimilars medicines on the list with reimbursed medicines should be granted based on a simplified assessment process of the medical technologies
   - Currently there is no difference in the assessment process of biosimilar medicines compared to the generic medicines, in order to grant the access on the list with reimbursed medicines. For this reason, we address the fact that biosimilar medicines should be subject to an assessment process (HTA), just as the innovative biological medicines. Starting from the premise that maximum benefits must be considered for patients, the existence of a distinctive and simplified HTA process for biosimilars, could provide an optimal use of these therapies according to their effectiveness and efficiency and would facilitate the patients’ access to these therapies.

6. Pharmacovigilance and traceability are essential to ensure the patients’ safety under treatment with biological medicines, as well as having functional registers of patients
   - From the perspective of the patients’ safety, monitoring the effects of treatment with biological medicines and emphasizing the importance of reporting these effects must be increased. The biological medicines (such as vaccines or the products derived from plasma) approved in the European Union after 2011 are marked by a black inverted triangle, that symbolizes the need for a careful monitoring by the physicians of the patients’ treatment with such medicines. This doesn’t mean that the medicine poses high risks, but encourages the reporting of possible secondary effects. The patients’ safety remains an essential element, the clinical tests being necessary and mandatory for every product, even if they have active components.
   - We also encourage the development of Registers of patients by therapeutic area, documents that could allow an easier monitoring of the number of diseased, of administered treatments, of observed effects, of treatment changes, but also of the costs involved in the medical act. In Romania this practise is still at the beginning, however a project of reference is The National Register of Patients with rheumatoid polyarthritis [3] that assumed the implementation at the national level of a system dedicated to the automate and more efficient measures of the complex process for the registration and monitoring of the files for over 4000 patients treated for different forms of rheumatoid polyarthritis.
7. There is a need to use an exclusive name for each biosimilar medicine, for a better identification of them

- The biosimilar medicines and the biological of reference are very different, therefore requiring a distinct name. This will make the patients and the physicians aware of the following: (i) the biosimilar is not an exact copy of the original biological medicine and (ii) they must read the instructions for the prescription of the biosimilar medicine. Moreover, having different names, it will be possible to find out if there is a difference in the efficacy and safety of the biosimilar product.

- This suggestion relies on the recommendations of the World Health Organization that proposes to mark the similar biological products with unique identification codes (Biological Qualifier [14]), distinct for every INN, so that the monitoring of the patients treated with such products to be done easier. In the event of such a system implementation by the World Health Organization and the European Medicines Agency (EMA), we will support the implementation of this system in Romania considering that it will lead to an increase in the patients’ safety providing a superior traceability.

8. It is necessary the total transparency in the information availability for biosimilar medicines in the Summary of Product Characteristics

- It is important that the attending physician to be able to identify easily, in the clinical section of the Summary of Product Characteristics what data was generated directly with the biosimilar medicine. His approval relies first of all on the qualitative / non-clinical comparative proofs, but it is also important for the physician to be completely informed on the reliability and efficiency of the data included in the direct comparative studies biosimilar – medicine of reference, as well as on the data included in the pivotal studies for the safety and efficiency of the medicine of reference.

- Therefore, we believe in the need for a transparent approach on the part of the regulatory authorities in terms of the Summary of Product Characteristics for biosimilar medicines that will be authorized and traded in the EU and implicitly, in Romania. We consider ideal that the Summary of Product Characteristics to include a combination of the data related to the biological product of reference (of its SPC) and of the data related to the biosimilar medicine. The biosimilar medicine SPC must include also data generated by the producing company of this medicine in the clinical development program during the period before authorization, which is the basis for granting the marketing authorization [15].

9. It is necessary to information the patients about the biological medication that they receive and to consult them for any modification of the therapy

- According to a consensus working paper of the European Commission in 2013: "It is important that the patients have a complex discussion with the attending physician about all the available therapeutic options, their safety, benefits and risks, as well as the differences between medicines, before they get to a decision in terms of the treatment" [16]. We support the principle that patients have the right to be informed about their medication and must be consulted if any changes of the treatment are made.

VI. CONCLUSIONS

The future of the therapies belongs to the biological treatments, either original or biosimilars. In March 2013, the American biopharmaceutical companies were developing more than 900 biological medicines that address over 100 diseases [17].

Local American Working Group (LAWG), the association of the pharmaceutical companies with American capital, leaders in research and biotechnology, together with Roche Romania, intends through the initiative of this document to contribute to raising awareness on biological medicines. The Local American Working Group and Roche position is in line with other numerous theses at the European level.

VII. Appendix 1: Legislation concerning biological medicines

European legislation:

- The Directive 2012/52/EC for the establishment of measures in order to facilitate the acknowledgement of medical prescriptions issued in another member state;
- The Directive 83/2001 related to the establishment of a Community code related to the medicines of human use;
- The European Commission Regulation no. 726/2004 for the establishment of community procedures related to the authorization and monitoring of medicines of human and veterinary use and of setting up a European Medicines Agency.

EMA Guides:

- The guide related to the biological similar products that include proteins derived from biotechnology, as active substance: non-clinical and clinical aspects (EMEA/CHMP/BMWP/42832/2005 Rev1);
- The guide related to similar biological medicines (CHMP/437/04 Rev 1);
- The guide related to the similar biological medicines that include proteins derived from biotechnology as active substance - quality problems (EMA/CHMP/PPV/247713/2012).

National legislation:

- HG 400/2014 (Government Decision) for the approval of packages of services and of the framework agreement that regulates the conditions of granting medical assistance within the healthcare insurance system for the years 2014-2015, Article 145;
- HG 124/2013 related to the approval of national healthcare programs for the years 2013 and 2014, Article 23;
- OMS/CNAS/619/300/2014, Order for the approval of Methodological standards for the implementation in 2014 of the Government Decision no. 400/2014 for the approval of packages of medical services and of the framework agreement that
regulates the conditions of granting medical assistance within the healthcare insurance system for the years 2014 – 2015, Article 5 para. 5;

- OMS 75/2009 for the Approval of Standards related to the calculation method of the prices for the medicines of human use;
- OMS 1301/500/2008 for the application of therapeutic protocols in terms of medicines prescription;
- CNAS (the National Healthcare Insurance System) Order No. 190 of March 29, 2013 for the approval of technical standards for the achievement of national curative healthcare programs for the years 2013 and 2014 (OPCNAS 190/2013, Article 30).

VIII. Appendix 2: Sources used

Association of the British Pharmaceutical Industry (ABPI) Position on Biosimilar medicines, mai 2014

EuropaBio, Guide to Biological Medicines. A Focus on Biosimilar Medicines


European Medicines Agency, What you need to know about biosimilar medicinal products, 2013

European Medicines Agency website / Human regulatory / Scientific guidelines / Biosimilar

European Medicines Agency, Questions and answers about biosimilar medicines (similar biological medicines), September 2012

European Medicines Agency, Human regulatory, Inspections, Good-manufacturing-practice and good-distribution-practice compliance

References

2. The Royal Society Publishing, Standardization of biological medicines: the first hundred years, 2006;
3. EMA, Întrebări și răspunsuri despre medicamentele biosimilare (medicamente biologice similare), sept 2012;
5. Pharmacy Practice News, Understanding the Difference between Biosimilar and Small Molecules Generics;
6. EMA, Întrebări și răspunsuri despre medicamentele biosimilare (medicamente biologice similare), sept 2012;
8. EMA website / Human regulatory / Scientific guidelines / Biosimilar
11. Studiul de caz YMENS TeamNet - Registrul national al pacientilor cu poliartrit reumatoidă, 2014;
http://www.who.int/medicines/services/inn/bq_improposal201407.pdf

Acknowledgements: The document was supported by the member companies of Local American Working Group pharmaceutical association in Romania: Abbvie, Amgen, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Glaxo Smith Kline, Janssen of Johnson & Johnson, Merck Sharp & Dohme, Novartis, Pfizer together with Roche Romania