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COMPARISON OF THE SAFETY PROFILE OF BIOSIMILARS WITH THEIR REFERENCE PRODUCTS

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The numbering of the tables and figures does not correspond to the same in the dissertation.

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ABBREVIATIONS USED

ADR	Adverse Drug Reaction
CQA	Critical Quality Attribute
EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency
ENCePP	European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
EPAR	European Public Assessment Report
EU	European Union
EV	EudraVigilance
EVWEB	EudraVigilance Web Portal
FDA	Food and Drug Administration
GVP	Good Vigilance Practices
HMA	Heads of Medicines Agencies
ICH	International Council for Harmonisation
INN	International Nonproprietary Name
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MH	Ministry of Health
MP	Medicinal Product(s)
MPHMA	Medicinal Products in Human Medicine Act
PASS	Post-Authorization Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred Term(s)
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SOC	System Organ Class
WHO	World Health Organization

1. INTRODUCTION

In the dynamic field of biopharmaceuticals, remarkable and transformative change is taking place, influenced, and accompanied by innovation and accessibility, technological experience, well-being of patients, and economic caution with medical advances. At the center of this shift is a particular category of therapeutics known as biosimilars that have the potential to change the pharmaceutical industry and healthcare significantly. This dissertation undertakes the engaging study of biosimilar medicinal products (MPs), delving into the critical aspect determining their future: pharmacovigilance.

With the expiration of patents of some highly successful biological MPs, a new category of drugs known as biosimilars has evolved. These biological products, which bear similarities to their original analogs but are competitively priced, have initiated a period of both potential and difficulty. The importance of biosimilars in increasing patient accessibility to vital treatments in the growing demand for cost-effective healthcare must be highlighted.

Some experts and regulators argue that the nuanced differences between biosimilars and reference biological products can have significant implications for patient safety and the long-term results of their use as a therapy. Regulatory authorities have, therefore, put in place strict guidelines to ensure comprehensive testing and evaluation before biosimilars can be authorized for use.

This work aimed to investigate the safety characteristics of biosimilars and their potential impact on the pharmaceutical industry and offer practical guidance to stakeholders to improve the procedures for marketing authorization, monitoring, and prescription of biosimilars.

The analysis starts with a detailed review of the legislative framework governing biosimilar MPs in the European Union (EU) since 2005. An essential part of the study is the detailed analysis of biosimilar MPs available on the European market from 04.2006 to 11.2022. It includes approved, rejected, and withdrawn biosimilars, offering a dynamic view of the progress of these complex biologics.

The dissertation work expands and evaluates additional pharmacovigilance monitoring for biosimilars and reference products. The study also assesses the safety information in the European

Public Assessment Reports (EPARs) and summaries of Risk Management Plans (RMPs) as of 11.2022.

Specific biosimilars were selected for more detailed analysis to ensure that the research work preserves accuracy and actuality. The main focus of the study is the analysis of individual case safety reports for adverse events in EudraVigilance (EV) as of 11.2022.

Each of these stages, distinguished by its specific challenges and opportunities, is methodically designed to help achieve the goals of the dissertation. This dissertation attempts to overcome the need for a systematic pharmacovigilance review of post-market biosimilars and improve scientific understanding and discussion on these complex biologics. The main objective of this work was not only to reveal empirical observations but also to make a valuable contribution to a broader dialogue on the impact of biosimilars on ensuring equitable access to critical medical interventions. By conducting in-depth analysis and providing reasoned recommendations, the aim is to promote the smooth inclusion of biosimilars in established therapeutic alternatives, thereby contributing to a health system that is both fair and effective.

2. AIM AND OBJECTIVES OF THE STUDY

2.1. Aim

This study aims to explore, compare, and analyze the regulatory framework and publicly available information regarding the pharmacovigilance monitoring of biosimilar MPs against their reference MPs authorized in the EU.

2.2. Objectives

In order to achieve the aim of the study, the following objectives have been set:

1. Study of regulatory requirements for the authorization of biosimilar MPs in the EU as of 11.2022:
   - Review and analysis of drug regulations regarding biological and biosimilar MPs in the EU, including Bulgaria.
   - Review and analysis of authorized biosimilar MPs in the EU from 04.2006 to 11.2022.
   - Review and analysis of biosimilar MPs with refusal or withdrawal of marketing authorization in the EU from 04.2006 to 11.2022, including the underlying motives.

2. Monitoring of biosimilar MPs and pharmacovigilance risks:
   - Analysis of biological and biosimilar MPs under additional monitoring in the EU as of 11.2022
   - Selection of biosimilar MPs authorized in the EU, for which public data are available as of 11.2022, intending to prepare a comparative analysis of the safety profiles between them and their reference biological products.
   - Comparative analysis of the public information on pharmacovigilance risks described in the selected biosimilars' EPARs.
   - Comparative analysis of the identified important risks, the identified potential risks, and the missing information from the RMP summaries of the selected biosimilars.

3. Analysis of the reporting of suspected ADRs for the selected biosimilars:

- Comparative and descriptive statistical analysis of the reported individual case safety reports for the selected biosimilars, published in the publicly accessible portal of the European database of suspected ADRs (adrreports.eu) as of 11.2022.
- Comparative analysis of publicly available information regarding the post-authorization safety studies (PASS) of the selected biosimilars as of 11.2022.

3. MATERIALS AND METHODS USED FOR THE PURPOSE OF THE STUDY

3.1. Materials

For this dissertation, materials and data have been used from:

- Regulatory regulation in the field of MPs in human medicine - regulations, directives, EMA guides, laws, and regulations;
- Working documents and analyses of international and national institutions, and expert organizations;
- Articles and works of leading authors and researchers in the field of drug policy in the EU;
- EMA database concerning EPARs and RMPs;
- The publicly accessible portal of the European database of suspected ADRs (adrreports.eu);
- The EU PAS Register.

3.2. Methods and methodology

➢ **Methods**

The following methods were used to achieve the purpose and objectives of this study:

- Documentary method – use of regulations, guidelines, and reports in the EU in biological and biosimilar MPs and monitoring of their pharmacovigilance.
- Historical analysis – traceability of biosimilars in the EU from 04.2006 to 11.2022
- Empirical method – comparison of different types of data regarding the pharmacovigilance of biosimilars from publicly available sources: EPARs, summaries of RMP, EVWEB, EU PAS Register, etc.

- Comparative analytical method – comparison of documents, guidelines, and reports in the EU regarding biological and biosimilar MPs and monitoring of their pharmacovigilance.
- Descriptive statistical analysis – systematization of data and results from publicly available sources.
- Graphical method – illustrating information and data through tables, figures, and graphs to help previous methods.

➢ **Methodology of analyzing databases**

- Methodology for the analysis of reference and biosimilar MPs under additional monitoring:

Information regarding the status of additional monitoring of reference and biosimilar MPs as of 11.2022 is derived from the EPARs of the products concerned.

- Methodology of analyzing EVWEB information:

The analyzed data are based on information from the publicly available European Database (adrreports.eu), which contains reports of suspected ADRs. This analysis is based on information from Section 1 and Section 4 of the European Database for suspected ADRs (EV via adrreports.eu). Section 1 presents the current total number of individual cases, and Section 4 visualizes the number of individual cases by groups of reactions. The current total number of individual cases in Section 1 represents the amount used to aggregate the spontaneous individual cases reported to the EV for a particular drug or active substance. The information in Section 4 shall consider the suspected adverse reactions reported on a case-by-case basis. As the same case may contain more than one suspected adverse reaction, the information in Section 4 does not reflect the total number of individual cases. However, it refers to the number of related adverse reactions. The number of individual cases shown in Section 4 depends on the number of reaction groups in each case. The same case appears as many times as the number of individual groups of reactions.

The analysis shall consider the period from the date of the marketing authorization of the selected MPs to the cut-off date of the data analysis, which is 12.11.2022. Based on the number of individual cases per reaction group and the current total number of cases as of 12.11.2022 for the

active substances of the selected products to be analyzed, the five system organ classes (SOCs) with the most individual cases by a group of reactions were selected. The number of individual cases per reaction group of these five SOCs for the reference and biosimilar MPs with these active substances and their current total number of individual cases was then determined. Active substances are present in the assay as, in some cases, the message was submitted only with the name of the active substance, and it is unclear whether the reference product or any of the biosimilars was used. The data obtained are presented in graphical form as a percentage of individual cases by reaction groups to the current total number of individual cases for active substances, reference products, and biosimilars.

- Methodology of analysis of the EU PAS register for reference and biosimilar MPs in the EU:

The EU PAS register, located on the website of the European Network of Centres in Pharmacoepidemiology and Pharmacovigilance (ENCePP), has been examined.

The search included the studies for the six active substances, and the cut-off date for registration of the studies was 12.11.2022. The studies were analyzed in three categories:

- Phase (finalized, ongoing and planned),
- Type (active monitoring, clinical study, observational study, etc.),
- Requirement against RMP (not applicable, EU RMP category 1, EU RMP category 2, EU RMP category 3, non-EU RMP).

4. RESULTS AND DISCUSSION

4.1. Study of regulatory requirements for marketing authorization of biosimilars in the EU

- **Review and analysis of drug regulations for biological and biosimilar MPs in the EU, including Bulgaria, as of 11.2022**

➢ **Regulatory documents in the EU**

The EU has developed a comprehensive regulatory framework for biosimilar MPs that includes several essential documents that clarify definitions, rules, and regulations, as well as procedures relating to the development, marketing authorization, and continuous pharmacovigilance monitoring of these products. This regulatory framework ensures that biosimilars meet stringent quality, efficacy, and safety standards while promoting competition and accessibility in the medicines market. By establishing clear guidelines and requirements, the EU has established a transparent and unified system that allows the timely marketing authorisation and availability of biosimilar MPs.

The centralized EU marketing authorization procedure ensures consistent evaluation and approval of biosimilar MPs across Member States. This procedure reduces duplication of effort and allows practical evaluation and approval of biosimilar MPs. In addition, the strict safety standards established by the centralized procedure reassure healthcare professionals and patients, assuring them that these products are as safe and effective as their more expensive analogs.

Table 1 shows the official names of these regulatory documents and a brief overview of their contents. Marketing authorization for MPs for human use is granted following a thorough scientific evaluation of their pharmaceutical quality, efficacy, and safety. The assessment shall be based on a benefit-risk analysis, and conclusive data shall be required to demonstrate that the benefits outweigh the risks. The marketing authorisation process ensures that MPs meet stringent standards and are subject to thorough scientific verification.

Table 1. Regulatory documents on biosimilar MPs in the EU

Regulatory document	Official title	Brief Description
Regulation (EC) No 726/2004	Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency	• Establishes the EMA and establishes a centralized authorization procedure for MPs, including biosimilars. • Establishes procedures for the authorisation and supervision of MPs, including biosimilar MPs, within the EU.
Regulation (EU) No 1235/2010	Amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced medicine products	• Specifies specific requirements for biosimilar MPs, including data on the marketing authorization dossier, comparative studies with the reference MP, and similarity data.
Directive 2001/83/EC as amended by Directive 2003/63/EC and Directive 2004/27/EC	Community code relating to medicinal products for human use	• Sets the framework for regulating MPs for human use in the EU. • It covers various aspects, including the definition and requirements of biosimilar MPs, marketing authorization procedures, naming, labeling, and pharmacovigilance monitoring. • To demonstrate similarity, introduce provisions for authorizing biosimilar MPs, including comparative data with the reference MP.

Biological MP obtained by biotechnological processes and set out in Annex I to Regulation (EC) No 726/2004 must be authorized for use by a centralized procedure. This procedure aims to improve access to these products in the EU Member States. Some biological MPs, such as polysaccharides (e.g., low molecular weight heparins), are an exception to this rule and may also

be authorized through other procedures, such as mutual recognition, decentralized, or national procedures.

- **Regulatory documents in Bulgaria**

Although national provisions do not regulate biosimilar MPs, several regulatory documents set out standard provisions for them:

- Medicinal Products in Human Medicine Act (MPHMA)
- Ordinance No 27 of 15 June 2007 on data requirements and documentation for marketing authorization and registration of medicinal products

Table 2 presents the official names of these regulatory documents and a brief overview of their contents.

Table 2. Regulatory documents regarding biosimilar MPs in Bulgaria

Regulatory document	Brief Description
Medicinal Products in Human Medicine Act (MPHMA)	• Regulates the regulation and control of MPs in Bulgaria. • Contains provisions on the authorization, registration, and supervision procedures of MPs, including biosimilars.
Ordinance No 27 of 15 June 2007 on data requirements and documentation for marketing authorization and registration of medicinal products	• Specifies requirements for the data and documentation to be submitted for authorization or registration, for extension, variation, and renewal of the marketing authorization or registration under a national, mutual recognition, and decentralized procedure for all types of MPs. • Appendix 10 sets out the specific requirements for the authorisation dossier for biosimilar MPs.

- **EMA Guides**

The scientific guides established by the EMA provide a comprehensive overview of the necessary criteria for developing and approving biosimilar MPs. These are divided into critical subgroups as described in this analysis and cover a wide range of topics. The scientific guidance provided by EMA is an essential source of information for all those involved in developing,

approving, or using biosimilar MPs. They create a solid basis for ensuring the safety and efficacy of biosimilar MPs in patients.

- **Comprehensive guidelines for biosimilar MPs**

This subgroup includes three guidelines, as described in Table 3. These guidelines describe the basic principles that apply to biosimilar MPs in Directive 2001/83/EC. They aim to provide a framework for developing, evaluating, and regulating biosimilar MPs in line with EU directives.

Table 3. EMA Comprehensive Guideline on Biosimilar LPs

Number	Current version	Effective date of the current version	Title
CHMP/437/04 Rev 1	1	30.04.2015	Similar biological medicinal products - Scientific guideline
EMEA/CHMP/BMWP/42832/2005 Rev1	1	01.07.2015	Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues - Scientific guideline
EMA/CHMP/BWP/247713/2012	0	01.12.2014	Similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues - Scientific guideline

- **Product-specific guidelines for biosimilars**

In addition to the general guidelines, the scientific groups at the EMA have also developed several product-specific guidelines that depend on the structure and classification of MPs. This subgroup includes a total of nine guidelines, which are detailed in Table 4. The purpose of these guidelines is to provide manufacturers with additional requirements and instructions for the development and approval of biosimilar MPs. They focus primarily on the non-clinical and clinical requirements for biosimilar MPs of the respective classes. The non-clinical section is concerned with pharmaco-toxicological requirements, and the clinical section includes the requirements for pharmacokinetic and pharmacodynamic studies as well as efficacy and safety studies.

Table 4. EMA's product-specific guidelines on biosimilar MPs

Number	Current version	Effective date of the current version	Title
EMEA/CHMP/BMWP/31329/2005	0	01.06.2006	Biosimilar medicinal products containing recombinant granulocyte-colony stimulating factor (Annex to guideline on similar biological

			medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues)
EMEA/CHMP/BMWP/118264/2007 Rev. 1	1	01.06.2017	Non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight heparins - Scientific guideline
EMEA/CHMP/BMWP/32775/2005_ Rev. 1	1	01.09.2015	Non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues - Scientific guideline
EMA/CHMP/BMWP/652000/2010	0	01.09.2013	Similar biological medicinal products containing interferon beta - Scientific guideline
EMA/CHMP/BMWP/403543/2010	0	01.12.2012	Similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues - Scientific guideline
EMEA/CHMP/BMWP/301636/2008 Rev. 1	1	01.01.2019	Similar biological medicinal products containing recombinant erythropoietins - Scientific guideline
EMA/CHMP/BMWP/671292/2010	0	01.09.2013	Similar biological medicinal products containing recombinant follicle-stimulating hormone - Scientific guideline
EMEA/CHMP/BMWP/94528/2005 Rev. 1	1	01.01.2019	Similar medicinal products containing somatropin (Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues) - Scientific guideline
EMEA/CHMP/BMWP/102046/2006	0	04.2009	Non-clinical and clinical development of similar biological medicinal products containing recombinant interferon alpha or pegylated recombinant interferon alpha - Scientific guideline

- **Other guidelines applicable to biosimilar MPs**

Several guidelines are not specific to biosimilar MPs but are relevant and applicable to this specific category of MPs. These guidelines ensure that biosimilar MPs maintain the same high safety and efficacy standards as reference MPs. This group includes four guidelines, which are listed in Table 5.

Table 5. Other guidelines applicable to biosimilar MPs

Number	Current version	Effective date of the current version	Title
EMEA/CHMP/BMWP/101695/2006	0	01.11.2007	Comparability of biotechnology-derived medicinal products after a change in the manufacturing process - non-clinical and clinical issues - Scientific guideline
CPMP/ICH/5721/03	0	06.2005	ICH Q5E Biotechnological/biological products subject to changes in their manufacturing process: comparability of biotechnological/biological products - Scientific guideline
EMEA/CHMP/BMWP/14327/2006 Rev 1	1	01.12.2017	Immunogenicity assessment of biotechnology-derived therapeutic proteins - Scientific guideline
EMA/CHMP/BMWP/86289/2010	0	01.12.2012	Immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use - Scientific guideline

- **Information guides, GVP modules, and reflection papers**

Finally, several documents were also analyzed, which do not fall into the above categories but still provide precious information on biosimilar MPs (Table 6). They contribute to a comprehensive understanding of the regulatory framework related to biosimilar MPs and help ensure their safety and efficacy on the market.

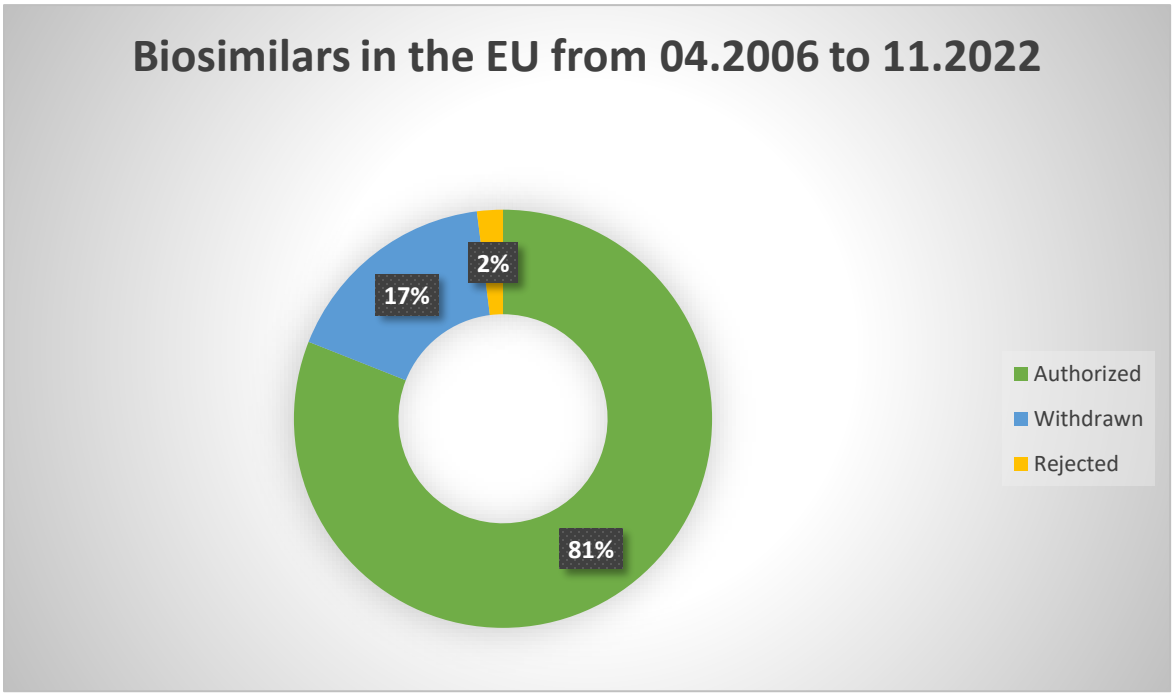
Table 6. Information guides, GVP modules, reflection papers

Number	Current version	Effective date of the current version	Title
-	-	02.10.2019	Information guide for healthcare professionals: Biosimilars in the EU
-	-	2016	Information guide for patients: What I need to know about biosimilar medicines
EMA/168402/2014	0	16.08.2016	Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations II: Biological medicinal products
EMA/627319/2022	-	21.04.2023	Statement on the scientific rationale supporting interchangeability of biosimilar medicines in the EU

- **Review and analysis of biosimilar MPs in the EU from 04.2006 to 11.2022**

The graph in Figure 1 visually represents the distribution of 90 biosimilar MPs in the EU regarding their authorization. The data cover the period from 04.2006 to 11.2022. During this period, 73 biosimilar MPs, representing 81% of the total, have successfully received marketing authorization (MA). Furthermore, it is essential to note that 15 biosimilar MPs, representing approximately 17% of the total, received MA but were subsequently withdrawn. On the other hand, only two products, representing 2 % of the total, were refused MA. Statistical data show a significant success rate in obtaining MA for biosimilar MPs within the specified period. This trend indicates the growing confidence in the safety and efficacy of biosimilar MPs among regulatory authorities. In addition, the low refusal rate for MA implies that manufacturers comply with the necessary quality standards and meet the strict requirements that regulatory authorities have established. This trend also suggests that the regulatory environment in the EU is favorable for the authorization of biosimilars.

Figure 1. Distribution of biosimilars in the EU concerning their marketing authorization status from 04.2006 to 11.2022



- **Biosimilar MPs authorized in the EU**

The European biosimilar MP market experienced a significant expansion between 04.2006 and 11.2022, mainly due to the increasing acceptance by healthcare professionals and patients and a favorable regulatory framework.

Figure 2. Distribution of the number of biosimilar MPs authorized in the EU from 04.2006 to 11.2022, by INN

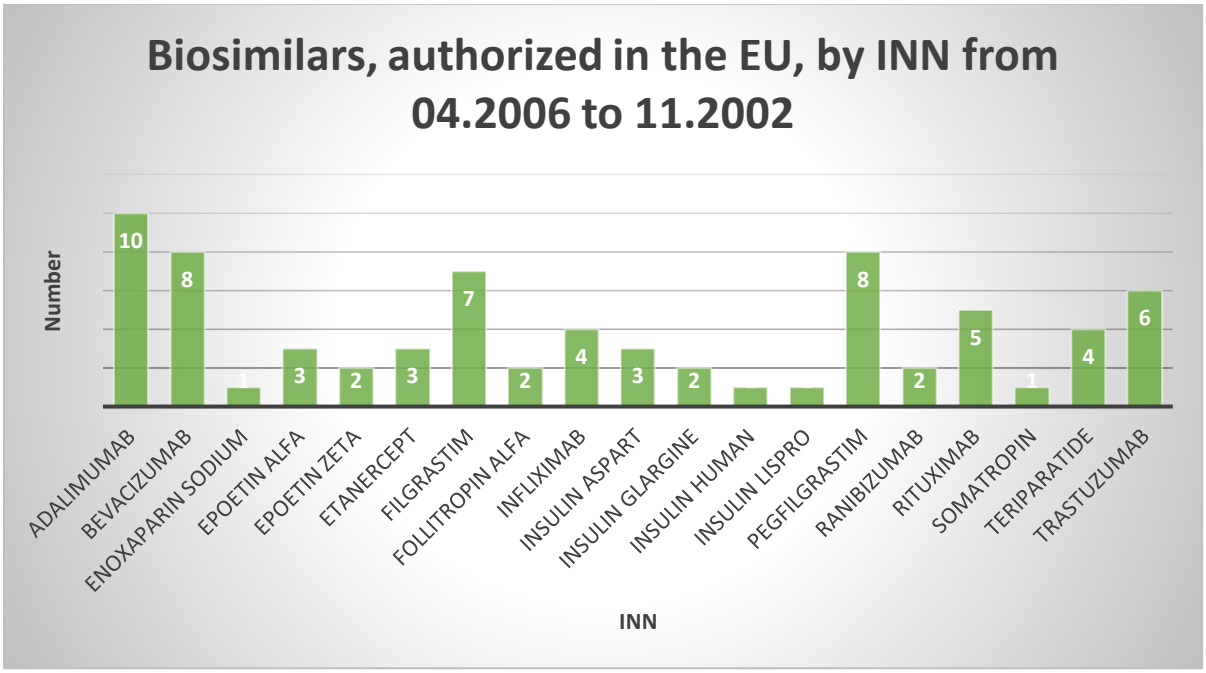


Figure 2 shows the distribution of biosimilars according to their INNs. During that period, 73 biosimilar MPs associated with 19 INNs were authorized. In 04.2006, the EC approved Omnitrope® (INN somatropin), making it the first biosimilar drug to receive such approval in the region. It is important to note that the average number of biosimilars per INN as of 11.2022 is 3.8 products. There are at least five biosimilar variants for six INNs: adalimumab, bevacizumab, pegfilgrastim, filgrastim, trastuzumab, and rituximab.

This phenomenon can be attributed to the widespread use of these active substances in the multiple therapeutic indications for which the relevant reference MPs have been authorized. Furthermore, the growing need for affordable therapeutic options has stimulated the development and availability of biosimilars related to these commonly used INNs. Of the products studied, adalimumab has the most significant number of biosimilar variants, a total of 10. In comparison,

it was observed that enoxaparin sodium, insulin human, insulin lispro, and somatropin had a relatively limited number of biosimilar analogs, with one option for each of these INNs.

Figure 3. Distribution of the number of biosimilar MPs authorized in the EU from 04.2006 to 11.2022 by year

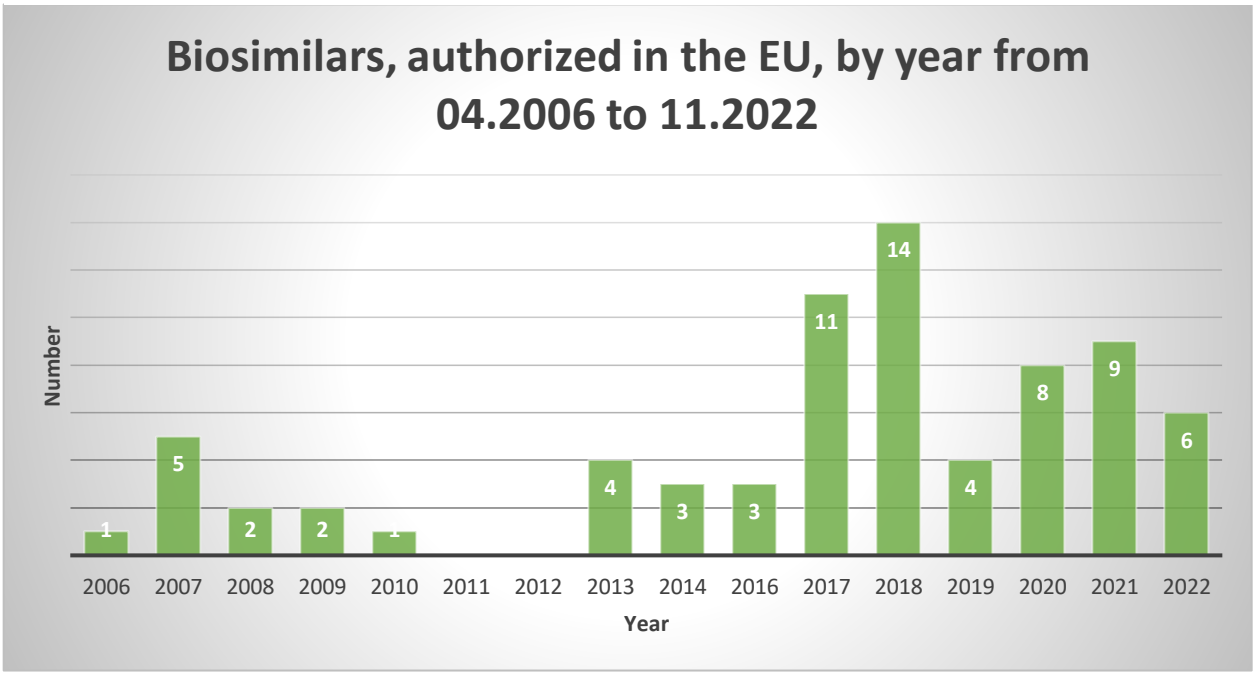
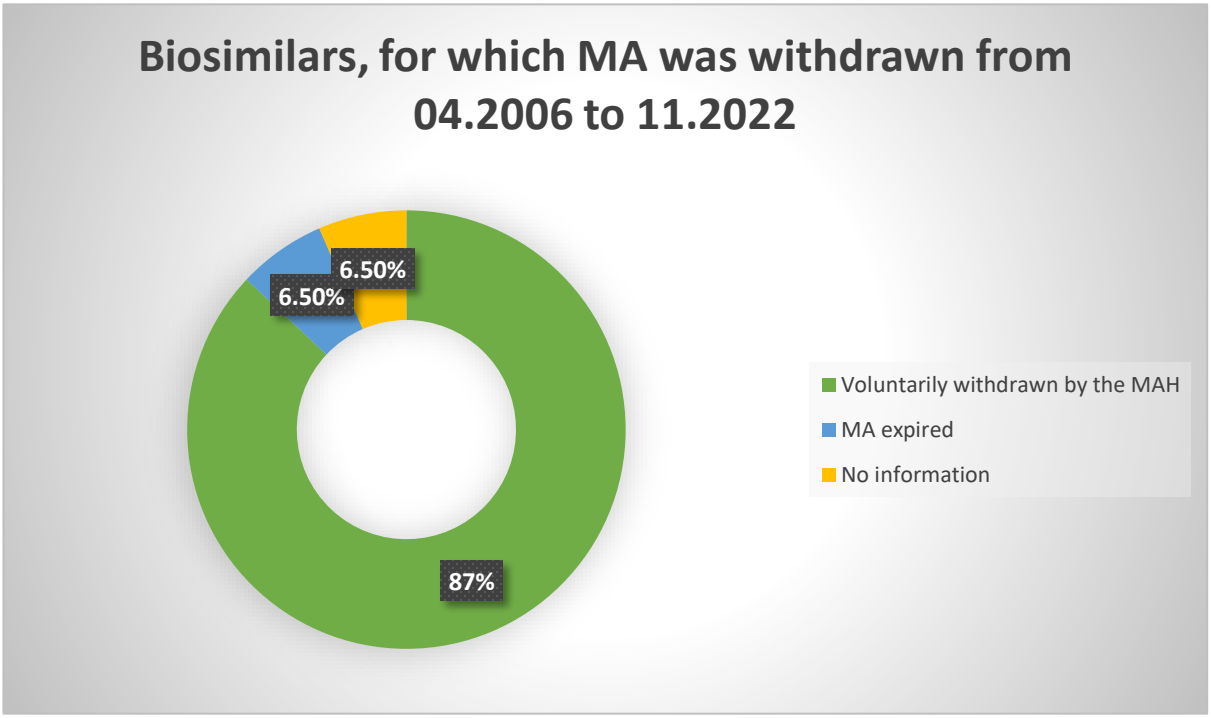


Figure 3 provides a visual representation of the distribution of biosimilar MPs concerning the year in which they received marketing authorization. The data show that a significant percentage of biosimilars, namely 71%, have received regulatory approval since 2017. The data suggest a growing trend in developing and approving biosimilars in recent years, reflecting the increasing adoption and demand for these cost-effective alternatives to reference MPs. Notably, no biosimilar MPs were approved in 2011 and 2012. In addition, 2006 and 2010 had the lowest number of approved biosimilar MPs, with one product for each of those years. On the other hand, 2018 had the most approved biosimilar MPs, a total of 14.

- **Review and analysis of biosimilar MPs in the EU with refusal or suspension of marketing authorization, including underlying motives**

The present study aims to analyze 17 biosimilar MPs whose MA has been withdrawn (n=15) or refused by the EMA (n=2) from 04.2006 to 11.2022. Figure 4 depicts the distribution of biosimilar MPs for which MA was withdrawn by the reasons for this. In most cases (87%, or 13 out of 15 products), the reason for withdrawal relates to a voluntary decision of the MAH, mainly motivated by commercial reasons. The MA for one product (6.5%) expired after three years, during which the product was not actively marketed. No justification was provided for withdrawing one of the products (6.5%). This research highlights the biosimilar MP market's complex nature and intense competition.

Figure 4. Distribution of biosimilar MPs for which MA was withdrawn from 04.2006 to 11.2022 by reasons for withdrawal



The analysis shows that two biosimilar MPs did not receive MA from EMA. For one of the products mentioned, problems with comparability, stability, and production process data have been identified. The refusal of MA for the other is due to problems related to the production process and quality. The study underlines the importance of ensuring that biosimilars meet the same safety

and efficacy standards as reference products. By maintaining strict regulatory requirements and adhering to good manufacturing practices, the MA process can effectively assess the suitability of these MPs for the market and ultimately protect public health.

The main reason for the withdrawal of most products can be correlated to commercial factors, highlighting the need for producers of biosimilar MPs to concentrate on strategic consideration and adaptability. It is worth noting that there is no product that has been withdrawn or rejected due to safety concerns or efficacy issues, which highlights the strict safety and efficacy criteria applied during the MA procedure in the EU. This underscores the commitment of regulators to protect public health and prioritize patient safety.

4.2. Pharmacovigilance monitoring of biosimilar MPs and associated risks

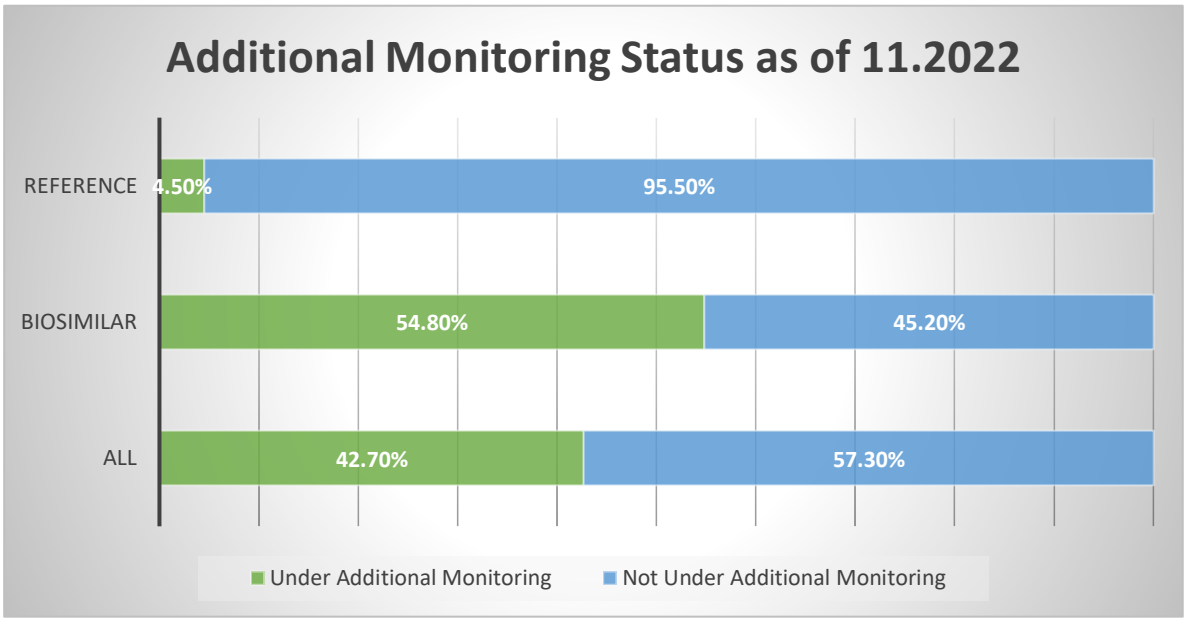
- **Analysis of reference and biosimilar MPs under additional monitoring in the EU as of 11.2022**

Like any other biological product, the reference (n=23) and biosimilar (n=73) MPs considered in this study are subject to additional monitoring by regulatory standards established by the EU. An in-depth review of publicly available EMA website data on reference and biosimilar MPs that are under additional monitoring as of 11.2022 was carried out.

The data presented in Figure 5 illustrate the results relating to the proportion of reference and biosimilar MPs subject to additional monitoring and those not subject to such monitoring. Furthermore, the figure provides an overview of all products considered collectively. The data show that more biosimilars (n=40) are subjected to additional monitoring compared to reference products (n=1). This phenomenon can be attributed to the fact that biosimilars are relatively new products on the market and have been granted MA after the expiry of patent protection for the reference product concerned. Most reference products are no longer included in this list, as the usual period for additional monitoring is five years from the date of the MA. On the other hand, biosimilars that are newer to the market are subject to continuous monitoring to ensure their safety and efficacy.

Notably, a significant proportion of biosimilars, namely 45.2% (n=33), are already excluded from the list. As of 11.2022, in the distribution of all MPs, the majority (n=96), representing 57.3% of the total, are not subject to additional monitoring.

Figure 5. Analysis of additional monitoring in reference and biosimilar MPs as of 11.2022



The presence of a significant number of biosimilar MPs that are further monitored indicates the innovative nature of biosimilar MPs as a pharmaceutical category. Nevertheless, some of these products are already excluded from the list for additional monitoring, suggesting their safety and efficacy. This suggests that the need for additional monitoring decreases as biosimilars continue to gain acceptance and establish a history of safety and efficacy.

- **Selection of biosimilars authorized in the EU for which there are sufficient public data as of 11.2022 to carry out a comparative analysis of safety profiles**

This study analyses publicly available data on the safety profiles of reference and biosimilar MPs that have been granted marketing authorization in the EU. The research was conducted using data obtained from EMA, particularly from the EMA website and the EV platform used for reporting of ADRs. This study examines 19 active substances (INNs) for which biosimilar MPs have been granted marketing authorization in the EU from 04.2006 to 11.2012.

The review covers three main categories of documents and information:

- European Public Assessment Report (EPAR): EMA issues an EPAR for each human or veterinary MP marketing authorization application. This report shall be prepared for MPs who have received or have been refused MA through the centralized procedure and shall serve as a means of disseminating relevant information on the product, including its evaluation carried out by EMA.
- Risk Management Plans (RMP) summaries: EMA has started publishing RMP summaries for MPs approved through the centralized procedure since 03.2014. This initiative represents a significant step towards greater transparency and broader public access to MP information. The RMP summaries represent valuable additional information, allowing stakeholders to increase their understanding of the risks and benefits associated with MPs.
- ADR messages submitted to the EV and then published on the publicly accessible EV portal (adrreports.eu): Since 2012, EMA has facilitated public access to information about suspected ADRs within the EEA. These reports are submitted electronically by both pharmaceutical companies and national regulatory authorities in the EV system.

Table 7 provides a comprehensive overview of data about the accessibility of documents and information in the three study areas (EPARs, RMP summaries, and ADR reports) for all 19 active substances.

Table 7. Data availability in EPAR, RMP and EV for the reference and biosimilar MPs

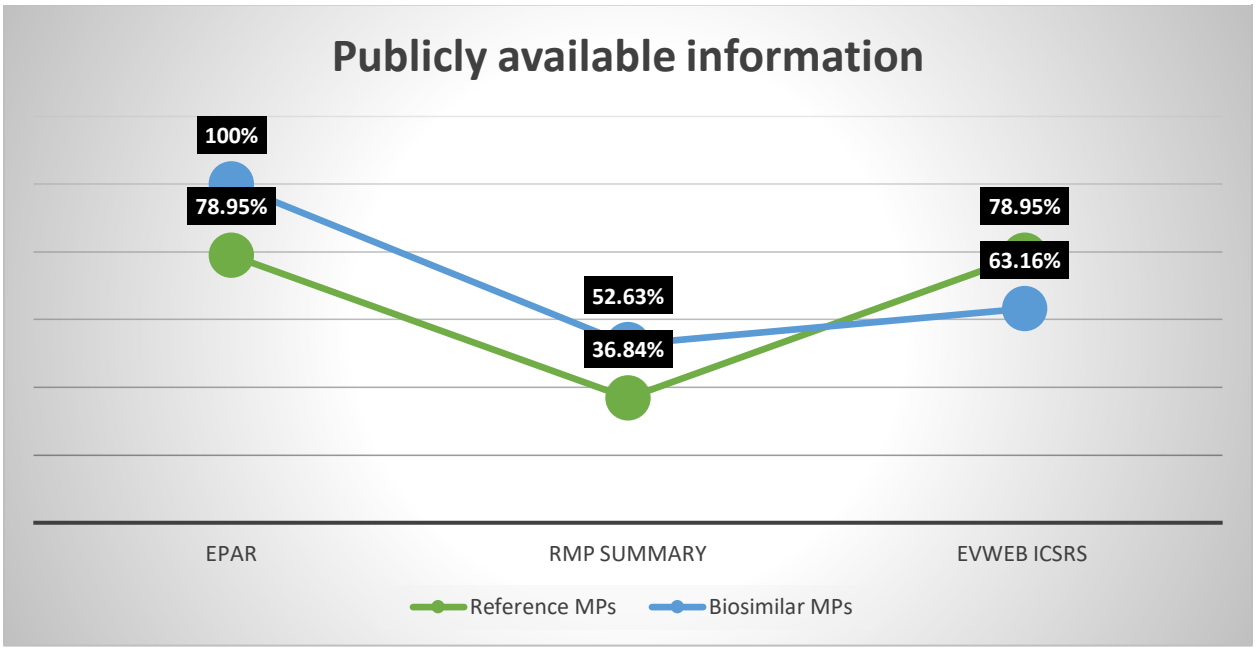
INN	European Public Assessment Report (EPAR)		Risk Management Plan (RMP) summary and available information on risks		Information on spontaneous reports of adverse drug reactions (over 500) in EV	
	RMP	BMP	RMP	BMP	RMP	BMP
Adalimumab	Yes	Yes	Yes	Yes	Yes	Yes
Bevacizumab	Yes	Yes	Yes	Yes	Yes	Yes
Enoxaparin Sodium	No	Yes	No	Yes	No	Yes
Epoetin Alfa	No	Yes	No	Yes	No	Yes
Epoetin Zeta	No	Yes	No	No	No	No
Etanercept	Yes	Yes	Yes	Yes	Yes	Yes
Filgrastim	No	Yes	No	No	No	Yes
Follitropin Alfa	Yes	Yes	No	No	Yes	No
Infliximab	Yes	Yes	Yes	Yes	Yes	Yes
Insulin Aspart	Yes	Yes	No	No	Yes	No
Insulin Glargine	Yes	Yes	No	No	Yes	Yes
Insulin Human	Yes	Yes	No	No	Yes	No
Insulin Lispro	Yes	Yes	No	No	Yes	No
Pegfilgrastim	Yes	Yes	No	Yes	Yes	No
Ranibizumab	Yes	Yes	Yes	Yes	Yes	No
Rituximab	Yes	Yes	Yes	Yes	Yes	Yes
Somatropin	Yes	Yes	No	No	Yes	Yes
Teriparatide	Yes	Yes	No	No	Yes	Yes
Trastuzumab	Yes	Yes	Yes	Yes	Yes	Yes

Figure 6 presents a comprehensive comparison of the results expressed in percentage for the reference and biosimilar MPs.

With regard to the EPARs, it has been observed that all assessment reports concerning the biosimilars included in the analysis are available. However, at the same time, only 78.95% of the assessment reports for the reference products are available. This difference in the availability of the reports raises questions about transparency and access to information on reference MPs. Moreover, the fact that all biosimilar MP reports are available implies a higher level of accountability and regulatory compliance.

The scope of disseminating RMP summaries and the risks described therein are significantly more limited than those of EPARs. Only 36.84% of summaries and associated risks are publicly available for reference MPs. This may mean that only some summaries have been submitted to the EMA, or the agency still needs to upload them on its website.

Figure 6. Analysis of publicly available pharmacovigilance information on reference and biosimilar MPs in the EU



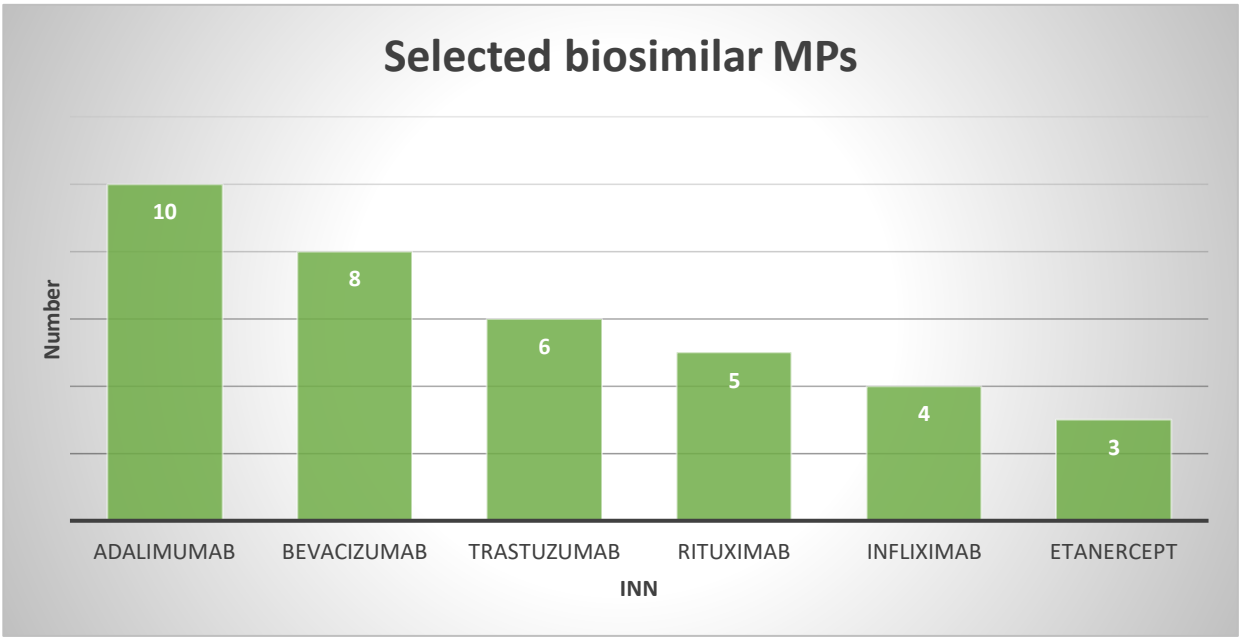
However, a much more significant proportion of the summaries is provided for biosimilar MPs, with 52.63% published. Clear rules are needed to improve the transparency and distribution of RMPs for all medicines, regardless of their classification.

The explanation for this phenomenon stems from the existence of the 2012 RMP requirement and the approval of a significant share of reference MPs before implementing this requirement. A significant proportion of biosimilar MPs needs to contain comprehensive details on their potential risks. This may be because biosimilar MPs are relatively new to the market and need more actual data to understand and document their potential risks fully. Therefore, regulators and manufacturers must cooperate and prioritize updating information in the RMP to ensure patient safety. The main objective of EMA is to publish RMP summaries for all MPs that have received approval for use through the centralized procedure.

A preponderance in the documentation of spontaneously reported ADRs is given to reference products for which there are more than 500 reports in the EV, representing 78.95% of all reference MPs.

The percentage for biosimilars is significantly lower - 63.16%. This is explained by the fact that biosimilars are authorized for use long after the reference ones because of patent rights, and therefore, their use could be more well distributed. In addition, healthcare professionals and patients must be made aware of these products, resulting in higher rate of ADR reporting. However, as more data on the safety and efficacy of biosimilar MPs become available and awareness of these products increases, their use and reporting of ADRs are also expected to increase.

Figure 7. Selected biosimilar MPs for subsequent analysis by INN and number



After looking at the public information data regarding the three criteria, six active substances (shown in Figure 7) were selected to be analyzed in more detail regarding their pharmacovigilance.

- **Analysis of the public information on pharmacovigilance risks described in the EPARs and RMP summaries for selected products as of 11.2022**

This section provides an in-depth overview of the safety risks of reference and biosimilar MPs described in the EPARs and the RMP summaries. This analysis evaluates the six selected active substances, examining information relating to their risks, indications, and other safety concerns. The results of this study provide valuable insights into the safety profiles of these products, allowing healthcare professionals to make informed decisions regarding their use. Furthermore, the study discusses potential gaps in existing information and distinguishes areas that require further investigation to ensure the continued safety of patients who use these MPs.

The study revealed that the average time interval between providing MA for reference MPs and the subsequent approval of their respective biosimilar MPs was 15.5 years. The time frame directly results from the regulatory requirements and patent provisions that govern the initial procedure for granting MA for biosimilar MPs. The duration between authorizations is the shortest for bevacizumab, with a period of 13 years, while rituximab indicates the most extended period, lasting over 17 years. The difference in time frames may be due to factors such as the complexity of the drug, the level of competition in the market, and the legal challenges faced by producers of biosimilar MPs. In addition, a more protracted process for the approval of biosimilar drugs may result from the need for extensive clinical trials and safety assessments to ensure the efficacy and safety of these products. Despite the long duration, the approval of biosimilars plays a crucial role in promoting competition and accessibility in the pharmaceutical industry.

Concerning the approved indications, it is essential to note that most biosimilar MPs are approved for the same indications as the reference MPs. The different products of bevacizumab show minor differences. The reference product was approved for use in 7 indications, while 6 were approved for 7 of the 8 biosimilar MPs. The exception is the lack of approval for the indication in advanced non-small cell lung cancer patients with activating mutations in the EGFR gene when combined with erlotinib.

The reference product for rituximab has received approval for 5 indications. Of the 5 biosimilar MPs, 2 received approval for 4 indications, except for severe rheumatoid arthritis, for which indication they had no approval.

The extrapolation principle can explain the correspondence of the indications. According to this principle, if a biosimilar demonstrates similarities to a reference medicine for a specific indication, it may receive MA in other indications of the reference medicine unless there are significant differences in the mechanism of action. This principle allows more efficient and cost-effective development of biosimilars, as it avoids the need for extensive clinical trials for each indication. However, it is essential to note that extrapolation is not always applicable and should be evaluated individually to ensure patient safety and efficacy.

The study of the risks to the safety of medicinal products in the EPAR shows that the data provided in this section coincides for the reference and biosimilar MPs. This is because the information in this section is derived from the SmPC of the relevant reference product. The SmPC content of the biosimilar MP shall correspond to the SmPC content of the reference MP. Therefore, the information in section "4.8. Adverse reactions" of the SmPC coincided for the reference and biosimilar MPs. Data are primarily derived from clinical trials conducted with the reference medicine. However, PASS results and Periodic Safety Update Reports (PSURs) must also be included to ensure up-to-date and accurate information. Including this information is crucial as it provides additional actual data on the safety profile of biosimilar MPs. This helps ensure that any potential adverse reactions or risks are accurately reflected in the SmPC, providing healthcare professionals with comprehensive and reliable information for prescribing and monitoring biosimilar MPs.

Establishing conformity between biosimilar MPs is essential to ensure their safety and efficacy, allowing healthcare professionals to make well-informed decisions about their use. Furthermore, the consistency of information between biosimilars and reference MPs fosters trust and inspires confidence among healthcare professionals and patients.

Examining the risks identified in the RMP summaries of the six active substances studied revealed no statistically significant differences. However, it should be noted that our analysis relies on a limited set of data, which requires further research to understand the risks associated with these active substances comprehensively. In addition, it is imperative that regulatory authorities maintain constant vigilance and regularly review RMP summaries in light of emerging information in order to comply with the safety standards associated with these RMPs.

There were no significant differences in the important identified and potential risks of the reference and biosimilar MPs for adalimumab. There are no long-term safety data for the reference (Humira®) as well as for two biosimilar MPs (Amgevita® and Hefiya®) in treating pediatric patients aged 6 to 18 years with ulcerative colitis.

The bevacizumab analysis posed challenges due to a lack of information on the important identified and potential risks in the reference product (Avastin®) and seven of the eight biosimilars. Among the available biosimilars, only Zirabev® has published data regarding the important identified risks that have been detected and the missing information.

Trastuzumab reports some differences in the three risk categories. The reference medicine (Herceptin®) and two biosimilars (Trazimera® and Ogivri®) are associated with three important identified risks: cardiac dysfunction, administration-related reactions, and oligohydramniosis. In addition, three other biosimilar MPs (Ontruzant®, Herzuma®, and Kanjinti®) carry two additional risks: haematotoxicity and lung disorders. One of the biosimilars (Zercepac®) has two risks consistent with the reference product while also mentioning an additional risk (hypersensitivity) missing from the other MPs. None of the biosimilar MPs showed the two important potential risks associated with the reference product: immunogenicity or hypersensitivity and anaphylaxis upon subcutaneous injection.

Furthermore, the short-term safety of subcutaneous administration compared to intravenous administration was not observed in any biosimilar MPs. Three of the biosimilars (Ontruzant®, Herzuma®, and Kanjinti®) noted cases of infections and medication errors, while only medication errors were found in one of the biosimilar MPs (Zercepac®). No risks are associated with the other two biosimilars, namely Trazimera® and Ogivri®. The missing information part also shows a discrepancy. Two risks were identified concerning the reference MP. The first risk concerns the long-term safety of the subcutaneous formulation compared to the intravenous formulation. The second risk involves the safety of the 75 mg docetaxel dose compared to the 100 mg dose. The risk in question was identified in three biosimilars MPs, namely Herzuma®, Kanjinti®, and Trazimera®. Three of the biosimilar MPs, namely Ontruzant®, Herzuma®, and Kanjinti®, are associated with an additional risk associated with the treatment of breast cancer in men. No missing information was reported for two biosimilar MPs, namely Ogivri® and Zercepac®.

The following findings were found for rituximab: Concerning the important identified risks, no differences are observed between the reference and biosimilar MPs, as all MPs have four identical risks. Two important potential risks for the reference product (MabThera®) have been identified: use outside the intended subcutaneous form and errors in the route of administration. One of the risks, in particular errors in the route of administration, was detected in each of the five biosimilar MPs. In four of the biosimilar MPs (Truxima®, Riximyo®, Rixathon®, and Blitzima®), three more risks were identified: malignancies, exacerbation of cardiovascular diseases and relapses of granulomatosis with polyangiitis and microscopic polyangiitis. In the fifth biosimilar MP, Ruxience®, only two risks are described: administration errors and relapses. The missing information in the reference and one of the biosimilar MPs (Ruxience®) describes one risk associated with long-term use in patients diagnosed with granulomatosis with polyangiitis and microscopic polyangiitis. The remaining biosimilar MPs describe another additional risk associated with administration during pregnancy and lactation.

The four important identified risks associated with the active substance infliximab are described in both the reference and the biosimilar MPs. All five MPs have one important potential risk, in particular colon cancer, and only one of the biosimilars (Flixabi®) shows an additional risk, namely immunogenicity. According to the available information, it can be concluded that the reference MP (Remicade®), as well as two of the biosimilar MPs (Flixabi® and Zessly®), have no risks described with the missing information. The remaining two biosimilars (Remsima® and Inflectra®) are associated with one risk, particularly long-term treatment with the subcutaneous formulation.

The study found no differences in the important identified risks (n=5) and the important potential risks (n=4) associated with etanercept between the reference and biosimilar MPs. The reference product is associated with a single risk within the missing information, namely immunogenicity, while no risks are described for the biosimilars.

Concerning the important identified risks, the data is consistent for four of the six active substances studied. The differences concerning one of the active substances, trastuzumab, are negligible. However, in the case of bevacizumab, the available data need to be more comprehensive to carry out a comprehensive comparison due to the lack of information on the risks of most products. The need for more available information relating to bevacizumab poses

challenges in conducting a comprehensive risk assessment when compared with other active substances. Further research and data collection are needed to assess the potential risks associated with bevacizumab comprehensively. The available data show consistency regarding the important potential risks associated with three active substances (adalimumab, bevacizumab, and etanercept). In contrast, the variations for the other three substances (trastuzumab, rituximab, and etanercept) are minimal. Nevertheless, minimum differentiations between trastuzumab, rituximab, and etanercept may necessitate meticulous assessment and monitoring because of their inherent risks. Further research is needed to gain a more comprehensive understanding of the exact risks associated with these three active substances. One to two differences in the risks associated with missing information were observed between the products for five of the six active substances. Furthermore, most products have not adequately stated the risks associated with bevacizumab.

The information relating to the pharmacovigilance risks of reference and biosimilar MPs is consistent in both EPARs and RMP summaries. This suggests that regulatory authorities have comprehensively assessed the risks associated with these active substances. However, it is imperative to maintain monitoring and undertake further research to understand the potential risks associated with these active substances thoroughly.

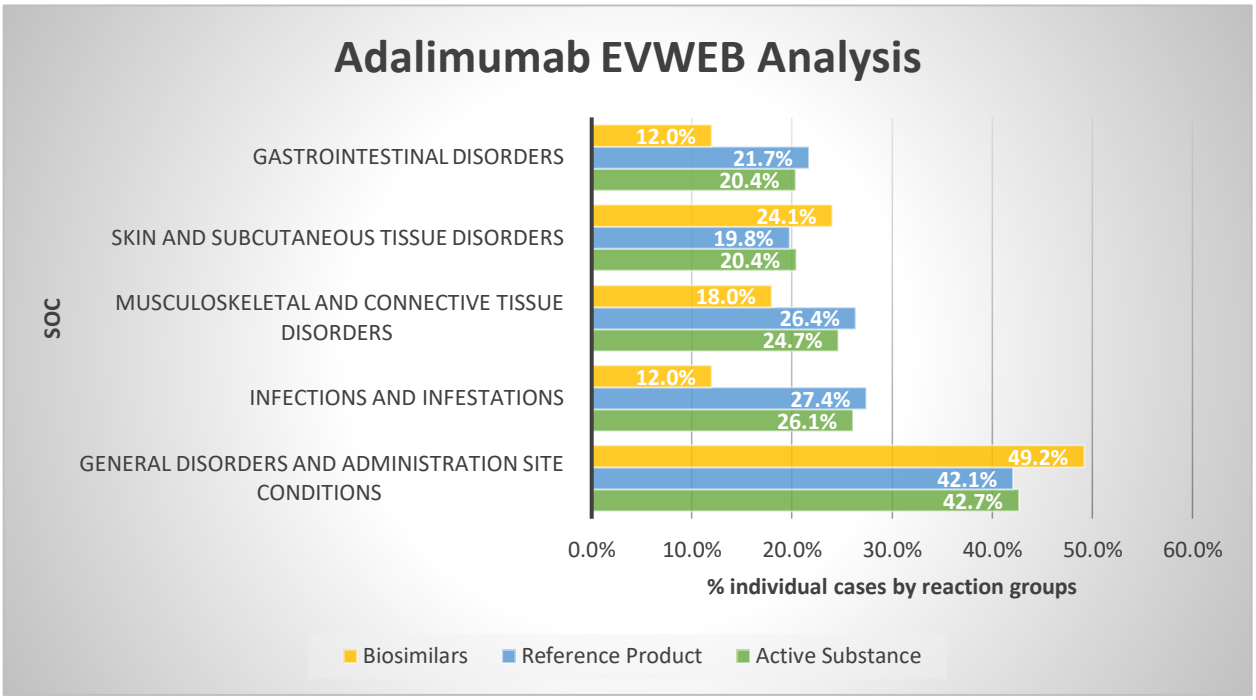
4.3. Analysis of adverse drug reactions in selected biosimilars

- **Comparative and statistical analysis of spontaneous ADR reports of the relevant selected LPs published in the publicly accessible EV portal (adrreports.eu) as of 11.2022**

  - **Adalimumab**

The study observed diversity in the total number of individual cases within the analyzed products. The active substance showed the highest number with a total of 89798 cases, followed by the reference product with 72772 cases and the biosimilar MPs with 8743 cases. Figure 8 shows the results for the five groups of reactions.

Figure 8. EVWEB analysis of the individual cases of ADRs with reference and biosimilar MPs with INN adalimumab



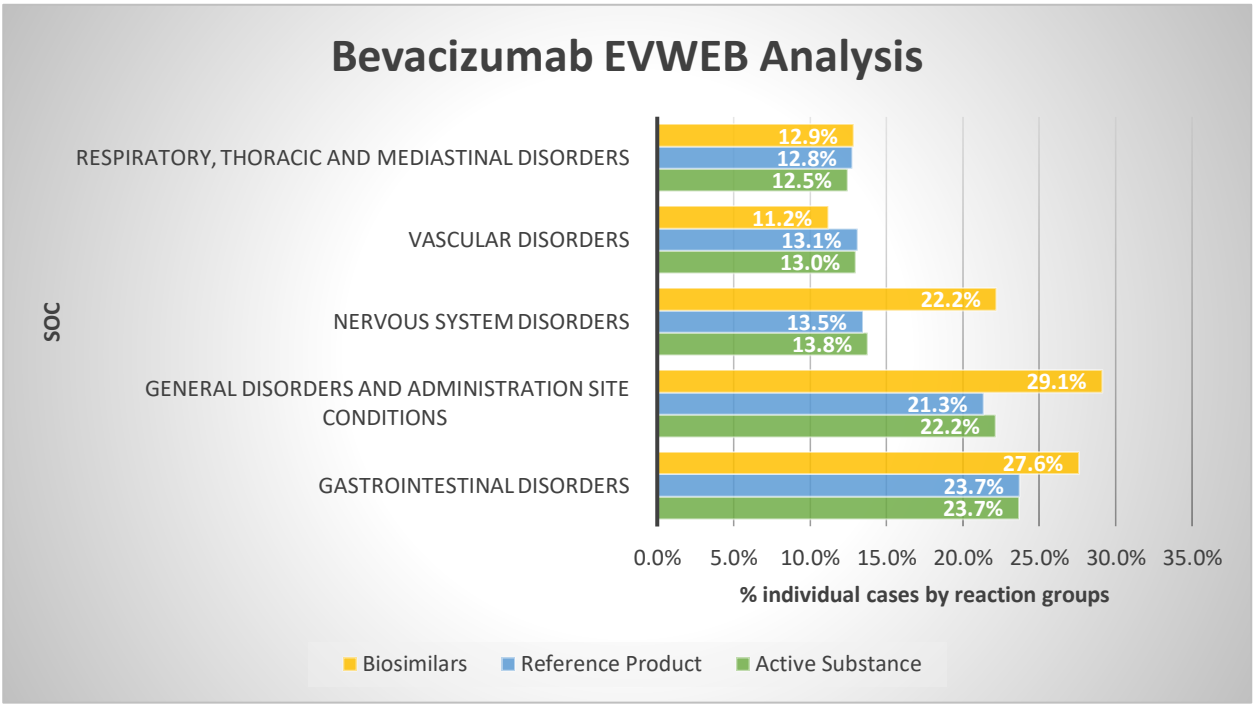
Remarkably, biosimilar MPs had a lower incidence than the active substance and the reference product in three of the five groups included in the study, with deviations ranging from -15.4% to -6.7%. Conversely, biosimilars reported more cases than the active substance and the reference product in two reaction groups, with deviations ranging from +3.7% to +6.5%. It is important to note that although the number of reported individual cases for biosimilar MPs is significantly smaller than the reference product, the observed deviations still fall within very narrow ranges, ranging from -15.4% to +6.5%. This observation highlights the similarity in reporting unexpected ADRs between the biosimilar MPs and the reference product, as well as the similarity in terms of safety and effectiveness. This suggests that biosimilar MPs are comparable to the reference product regarding their safety and efficiency profiles. In addition, these findings provide further evidence of the rigorous process of evaluation and approval of biosimilar MPs by regulatory authorities, ensuring that they meet the same high standards as the reference product. The relatively lower number of cases of biosimilar MPs can be attributed to the recent marketing authorization of these products, leading to their limited acceptance and prescription compared to

the reference product. It is expected that the use of biosimilar MPs will increase both the frequency of reporting and the number of individual cases in the coming years.

- **Bevacizumab**

The results for bevacizumab are shown in Figure 9. Data analysis showed that the active substance had the highest reported total number of individual cases (n=48639), followed by the reference product (n=37821) and biosimilars (n=707).

Figure 9. EVWEB analysis of the individual cases of ADRs with reference and biosimilar MPs with INN bevacizumab



In one of the five reaction groups, the biosimilar MPs showed a lower incidence of cases than the active substance and the reference product, with slight deviations of about -2%. Compared to this, the percentage of observed cases in four groups of reactions was higher for biosimilars compared to the active substance and the reference product, with deviations between +0.1% and +8.7%. The data for the reference product are very close to those for the active substance, mainly due to the higher volume and the more significant similarity in the number of individual cases. This phenomenon is probably because the reference product has been on the market for longer and has been used by more patients. Despite the significantly smaller number of individual cases

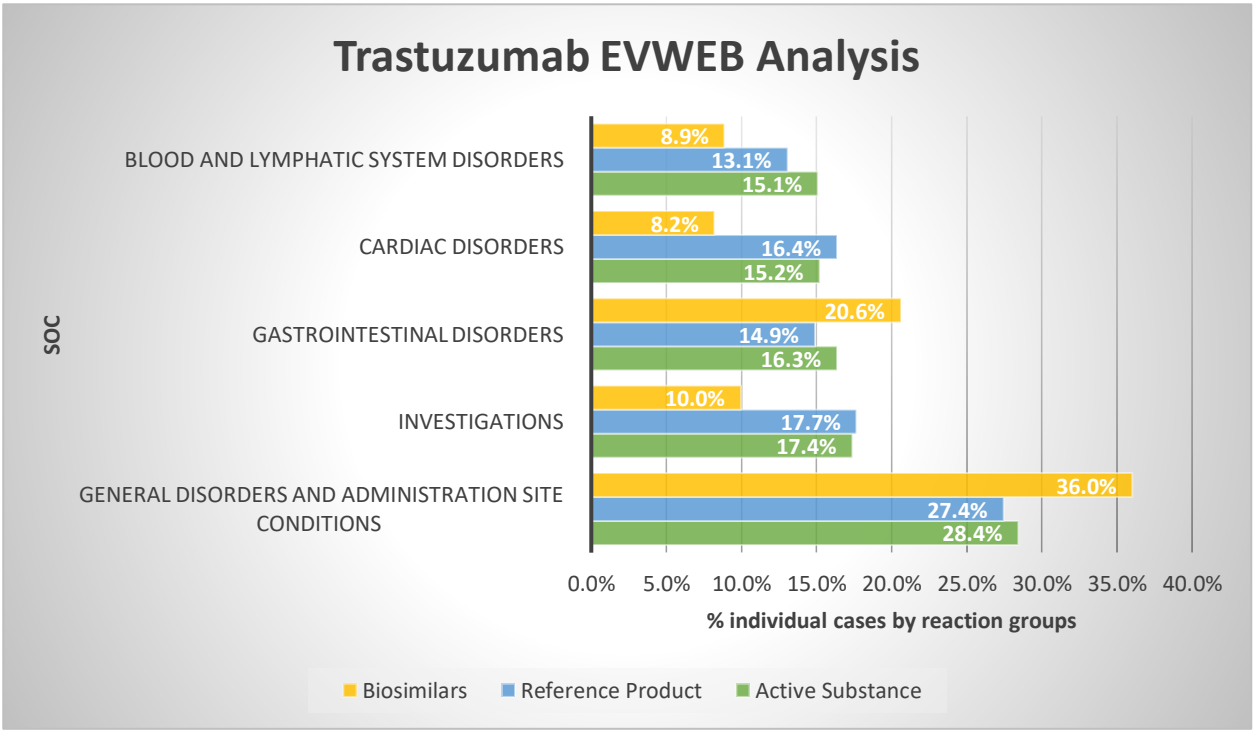
reported for the biosimilars, the differences remained relatively limited, ranging between -1.9% and +8.7%.

- **Trastuzumab**

The results showed that the active substance had the highest total number of individual cases (n=30709), followed by the reference product (n=21788) and biosimilars (n=1194). Figure 10 depicts the results. In three of the five reaction groups, biosimilars reported fewer cases of the active substance and the reference product, with differences between -8.2% and -4.2%. In two reaction groups, biosimilars showed more cases than the active substance and the reference product, with differences ranging from +4.3% to +8.6%.

While the number of cases for the reference product is closer to that for the active substance compared to the biosimilars, the differences remain within a relatively narrow range, ranging from -8.2% to +8.6%. This fact demonstrates that reporting spontaneous ADRs in biosimilars is not significantly different from that for the reference product. Combining these observations, the study highlights consistency in ADR reporting in biosimilars compared to the reference product.

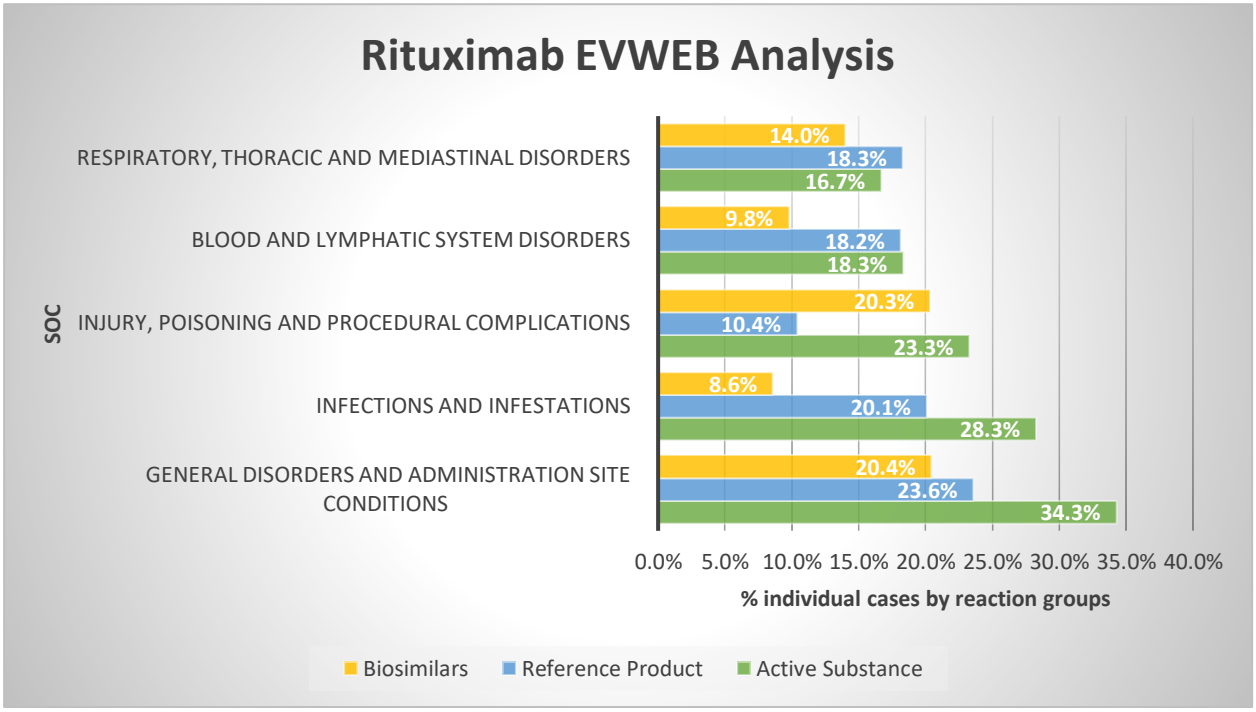
Figure 10. EVWEB analysis of the individual cases of ADRs with reference and biosimilar MPs with INN trastuzumab



- **Rituximab**

The results showed that the active substance had the highest number of individual cases (n=73605), followed by the reference product (n=24375) and biosimilars (n=3703). The results are presented in Figure 11.

Figure 11. EVWEB analysis of the individual cases of ADRs with reference and biosimilar MPs with INN rituximab

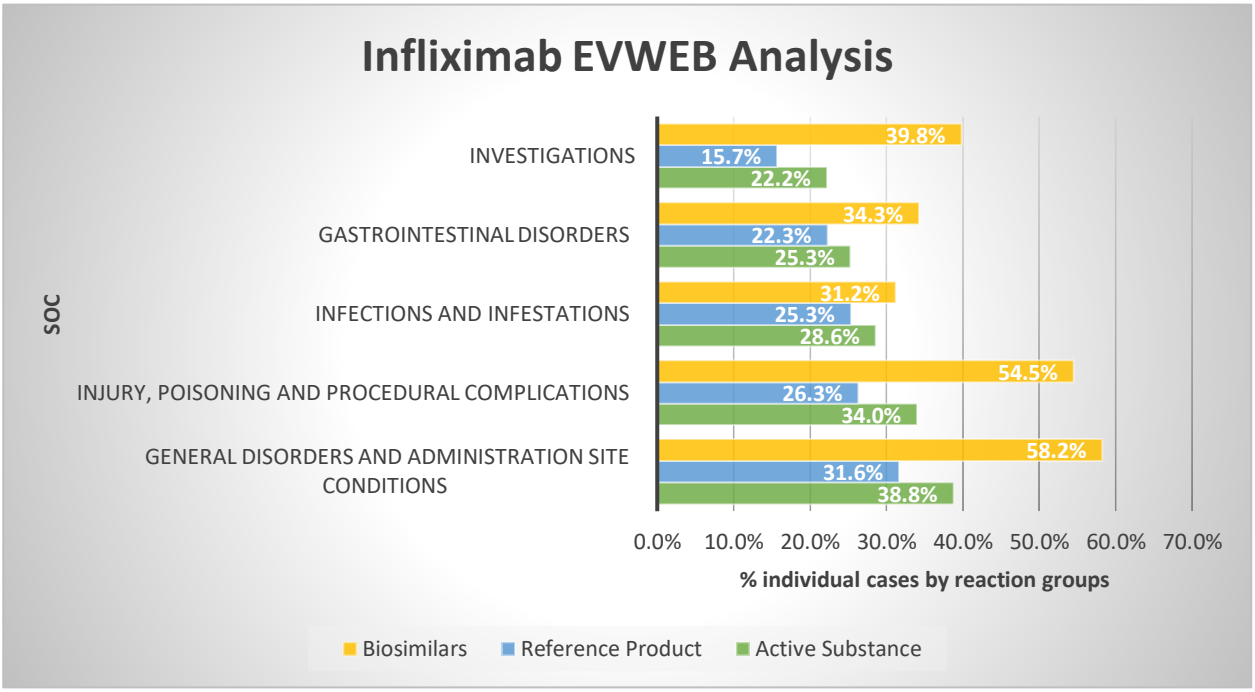


In most reaction groups, the biosimilar MPs reported fewer cases from the active substance and fewer from the reference product. The observed differences varied between -19.7% and -2.7%. Within one of the groups of reactions, it was observed that the cases associated with biosimilars exceeded those of the reference product by a difference of +9.9%. Although the number of cases for the reference product is closer to that of the active substance than biosimilars, the differences remain within a relatively narrow range, ranging from -19.7% to +9.9%. This highlights that the reporting of spontaneous ADRs for biosimilars is similar to that for the reference product. This suggests that the biosimilars and the reference product have similar safety profiles concerning ADRs. However, it is essential to continue monitoring and reporting ADRs to ensure patient safety and trust in using biosimilars.

- **Infliximab**

The current total number of individual cases for infliximab is highest for the active substance (n=117066), followed by the reference product (n=74459) and biosimilars (n=18356). In Figure 12, the results for the five groups of reactions are plotted.

Figure 12. EVWEB analysis of the individual cases of ADRs with reference and biosimilar MPs with INN infliximab

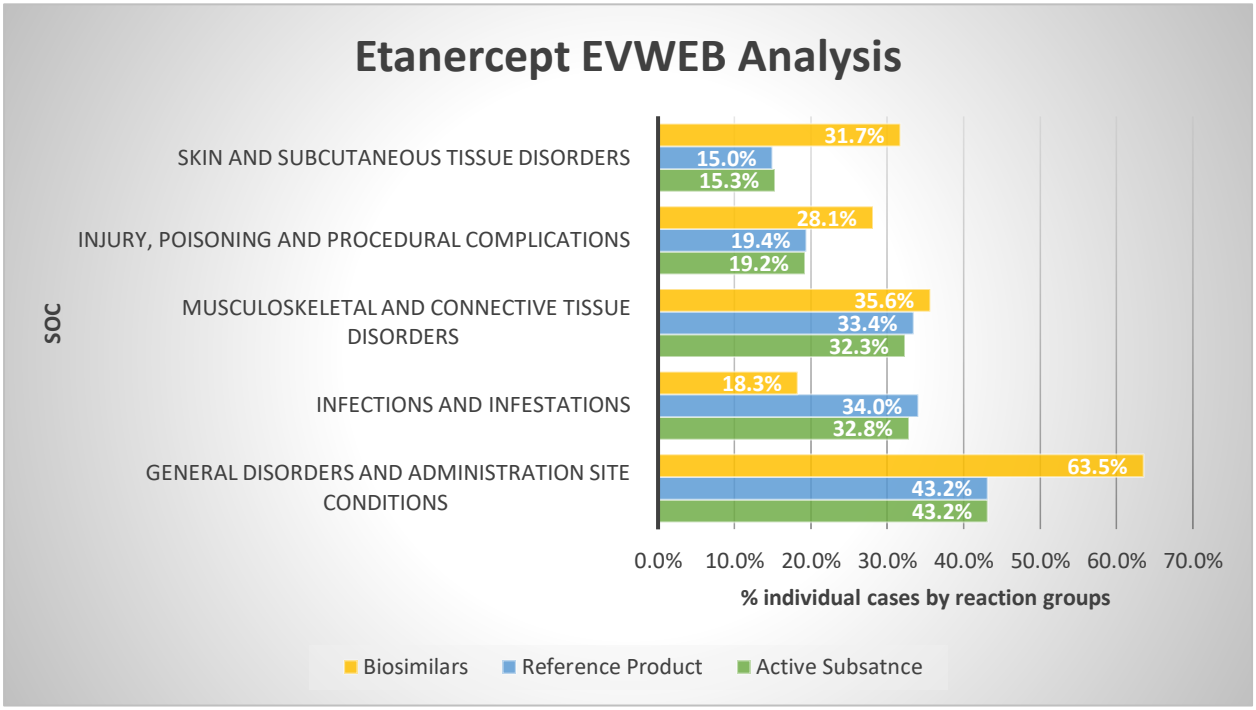


In five reaction groups, biosimilars had more cases than the active substance and the reference product, with differences between +2.6% and +28.2%. The data for the reference product are much closer to those for the active substance. Despite the significantly lower number of individual cases in biosimilars, the differences remained within a relatively narrow range, ranging between +2.6% to +28.2%. This indicates that the reporting of spontaneous ADRs in biosimilars is not significantly different from that for the reference product.

- **Etanercept**

The current total number of individual cases for etanercept is highest for the active substance (n=119715), followed by the reference product (n=106950) and biosimilars (n=5993). Figure 13 depicts the distribution of individual cases in the five groups of reactions.

Figure 13. EVWEB analysis of the individual cases of ADRs with reference and biosimilar MPs with INN etanercept



In one of the five reaction groups, biosimilars had fewer cases than the active substance and the reference product, with differences between -15.7% and -14.5%. In four reaction groups, biosimilars had more cases than the active substance and the reference product, with differences ranging between +2.2% and +20.3%. As with other products, the data for the reference product are much closer to those for the active substance. Despite the significantly lower number of individual cases in biosimilars, the differences remain within relatively narrow ranges, ranging between -15.7% to +20.3%. This indicates that the reporting of spontaneous ADRs in biosimilars is not significantly different from that for the reference product.

- **General analysis**

Comparative analysis of the reported ADR cases showed that for all six product groups, the highest number of individual cases was reported for the active substance, followed by the reference product, and the lowest number of reported cases for biosimilar MPs. Several factors can explain this trend.

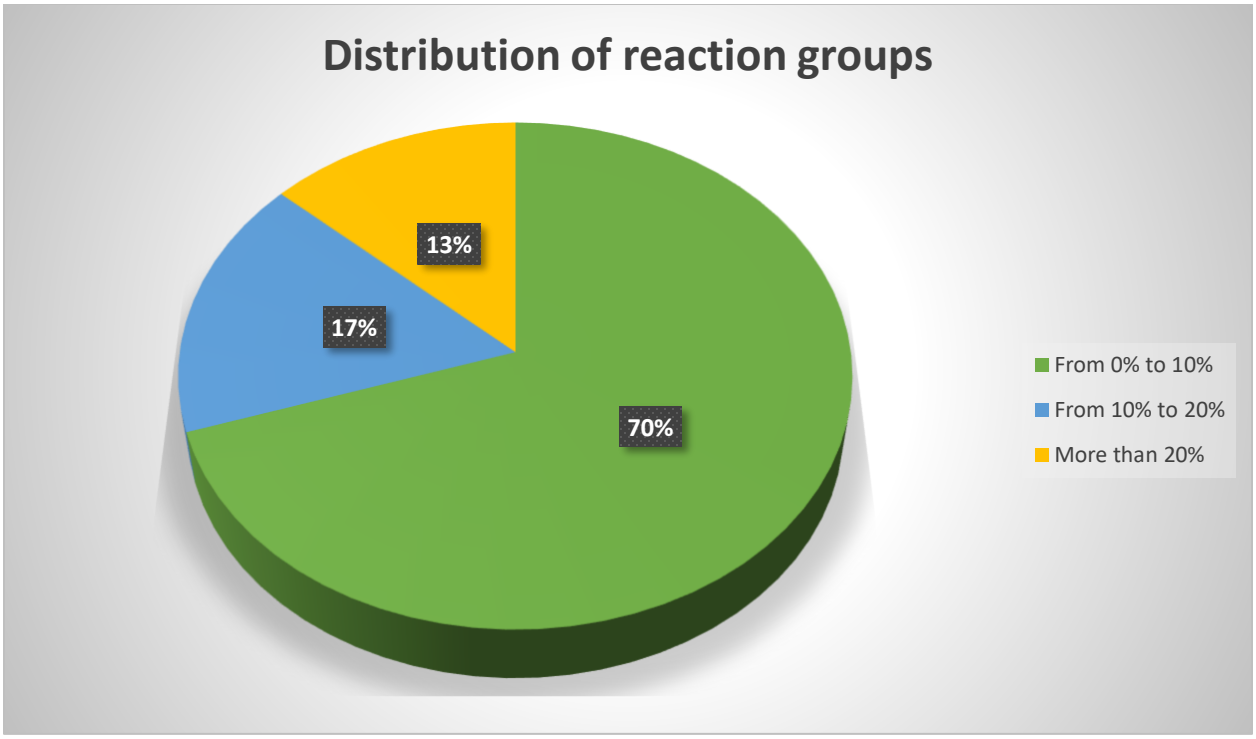
First, the cases reported for the active substance cover the entire database for that substance, including the cases for the reference product and biosimilars, as well as those where the specific product cannot be identified. The traceability problem for reference and biosimilars is well known and is supported by the encouragement to report the exact trade names and batches of products together with ADRs.

Secondly, reference products have been on the market for much longer, as they are innovative, whereas biosimilars can be marketed after the patent of reference products expires. For this reason, reference products are preferred when prescribed, resulting in more patients using the reference products and individual case reporting becoming significantly more extensive.

Once the number of reported ADRs for the reference products approaches that of the active substance, the differences between these two groups become significantly smaller. Interestingly, despite the significant difference in the number of reported cases for the reference and biosimilar MPs, the differences in reporting in the analyzed reaction groups lie within relatively narrow limits. The distribution of the number of reaction groups by degree of difference between biosimilars and reference products is presented by the visualization in Figure 14.

This underlines that most of the reaction groups (70%) fall within the lowest range of 0 to ±10%, followed by the ±10 to ±20% range, and the reaction groups with the highest degree of difference (±20%) are the least common. The most significant differences are noted in infliximab (±20% in three reaction groups) and etanercept (±20% in one of the reaction groups). The integrated analysis of reported individual ADRs in reference and biosimilar MPs demonstrates that the two types of products have similar safety profiles concerning spontaneous ADRs.

Figure 14. Distribution of reaction groups by difference interval in the number of ADRs of the respective reaction group between reference and biosimilar MPs



- **Comparative analysis of publicly available information regarding post-authorization safety studies (PASS) for selected biosimilars as of 11.2022**

As with any new medicine, for biologics and biosimilars it is essential to monitor their safety in the post-marketing environment. PASSs are conducted after regulatory agencies have authorized the biological or biosimilar to gather further information on its safety.

This study aims to review the current status of PASSs for the selected six active substances by looking at the different types of PASSs that take place on these substances. The methodology of the analysis is described in Section 5. Methods and methodology.

Figure 15 depicts PASS distribution by phase (completed, ongoing, or planned studies) for the six active substances. We observe that adalimumab and infliximab stand out with the highest number of studies performed (n=23), followed by rituximab (n=14), etanercept (n=13), and bevacizumab and trastuzumab (n=11). Despite the diversity in the number of studies, unmistakable

trends in their dynamics emerge. In four of the six active substances (adalimumab, rituximab, infliximab, and etanercept), the ongoing studies predominated (n=13, 9, 11, 7, respectively), followed by the completed ones (n=7, 3, 9, 4, respectively), while the planned studies were the least (n=3, 2, 3, 2, 2, respectively).

The study dynamics differ for the other active substances, bevacizumab and trastuzumab. In this case, the completed studies have a higher share (n=6 and 5, respectively), followed by the continuing ones (n=4 and 3, respectively). The planned studies are fewer (n=1 and 3, respectively).

Figure 15. Analysis of PASS by phase as of 11.2022

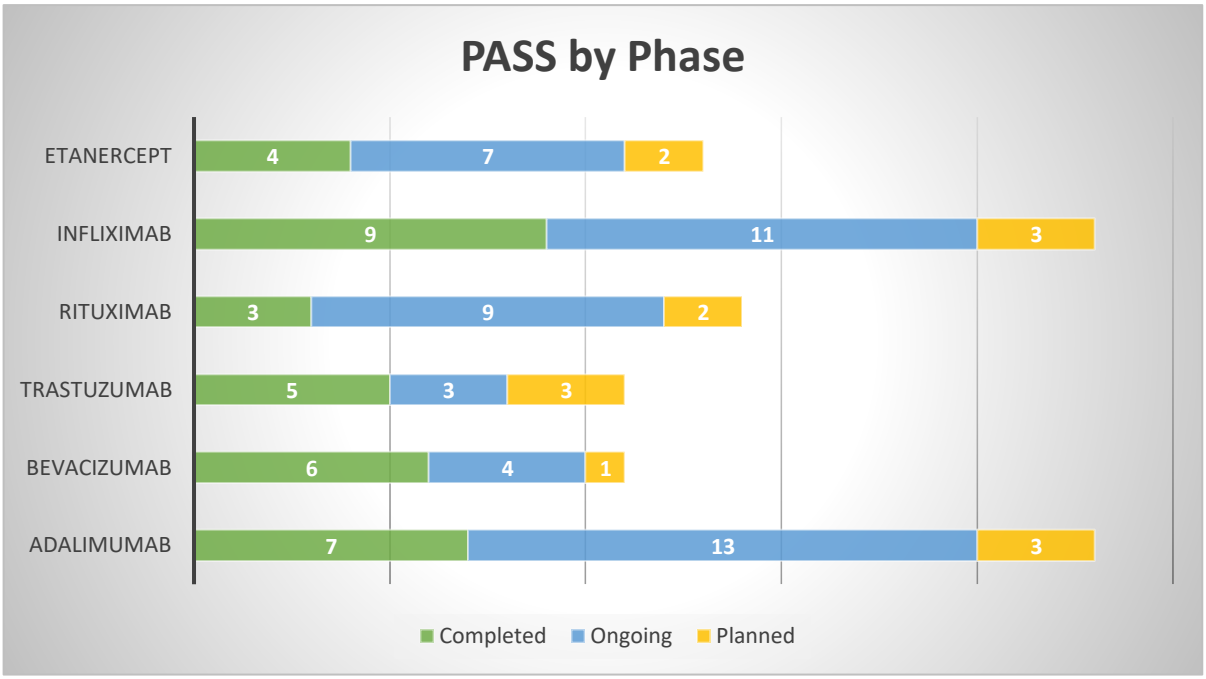
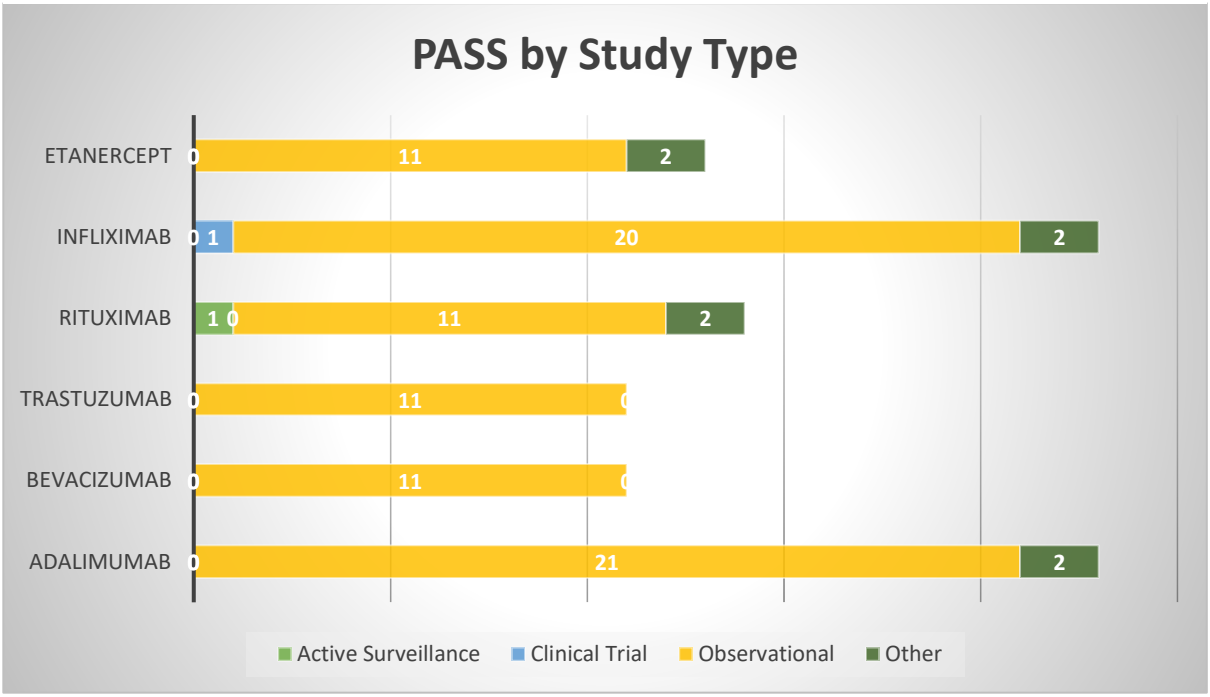


Figure 16 provides the results of analyzing the study types (active monitoring, interventional clinical trials, observational studies, and others) in the six active substances. It is noticeable that observational studies dominate additional safety monitoring in the six active substances. In particular, bevacizumab and trastuzumab showed no other type of studies performed (n=11). For the other four active substances, adalimumab, rituximab, infliximab, and etanercept, the number of studies of type others was two for each active substance.

Figure 16. Analysis of PASS by study type as of 11.2022

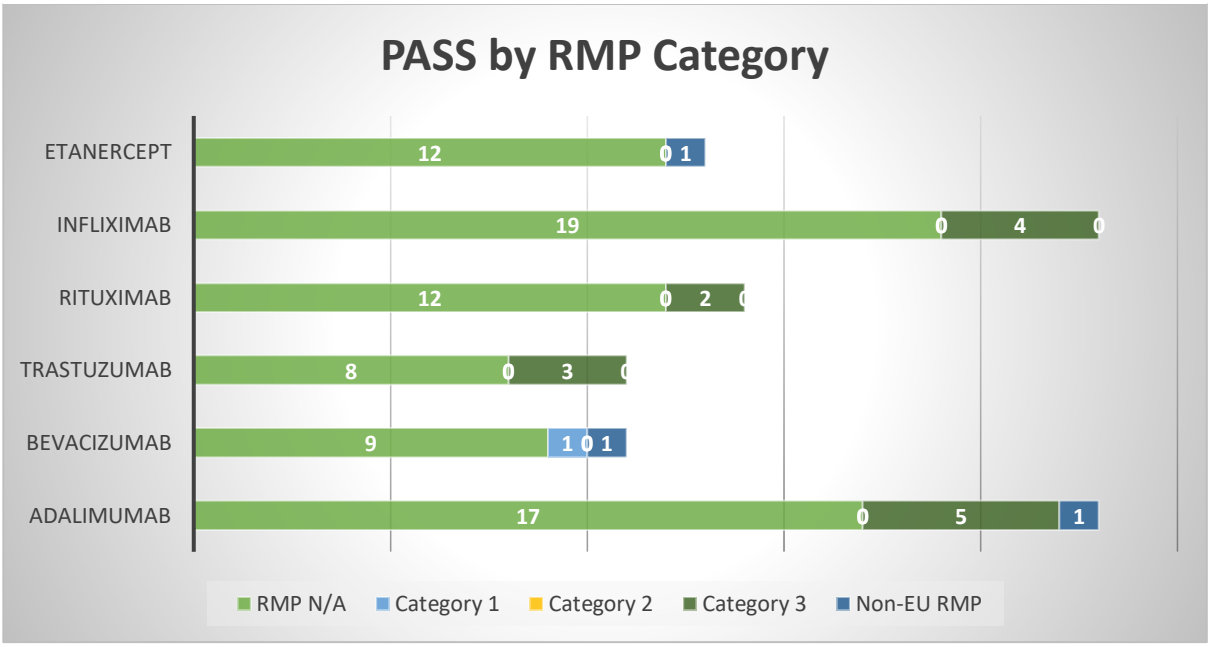


It is interesting to note that only one interventional clinical trial is found in infliximab. In addition, a single study with active monitoring has been documented in rituximab.

Figure 17 provides the results of the distribution of the studies against the requirements of the RMP. Of great importance is the fact that the majority of studies on the six active substances have been found to have no application to the requirements laid down in the RMP.

Analyzing this issue in more detail, it is noted that studies (n=5, 3, 2, and 4) belonging to category 3 of the RMP exist in the four active substances adalimumab, trastuzumab, rituximab, and infliximab. This type of study does not fall under category 1 or 2 but is required as part of the pharmacovigilance plan for authorized medicinal products.

Figure 17. Analysis of PASS by category of RMP as of 11.2022



Of particular importance is that only one study of category 1 of the RMP was noticed in bevacizumab. This type of research may be imposed as a condition of marketing authorization as it is crucial to the product's benefit/risk profile.

Last but not least, three studies (in adalimumab, bevacizumab, and etanercept, respectively) were found that were not related to EU risk management plans but were conducted outside the EU. This fact reflects the interest and importance of research beyond EU borders, highlighting the global aspect of scientific efforts to monitor biologics' safety and their biosimilar analogs further.

5. CONCLUSIONS AND RECOMMENDATIONS

5.1. Conclusions

The study of the safety profiles of biosimilar MPs compared to their reference products within the EU provides significant information on the regulatory framework and public health implications. It plays a crucial role in ensuring biosimilar MPs' quality, efficacy, and safety before and after their marketing authorization in the EU. Furthermore, understanding the safety profiles of biosimilar MPs helps healthcare professionals make informed decisions when prescribing these products to patients.

This dissertation explains many essential findings that reflect the current development and regulation of biosimilar MPs within the EU.

- **Well-established legislative framework:** One of the critical findings of this work is the imposed regulatory framework that effectively regulates biosimilars within the EU. Over time, regulatory authorities have diligently established a well-defined and comprehensive legislative framework for developing and marketing authorization of biosimilars, which is subject to continuous development and improvement, to ensure that biosimilar producers comply with strict safety and efficacy criteria.
- **Growing interest and extent of marketing authorization:** The increasing level of interest in biosimilar MPs within the EU serves as evidence of the effectiveness of the regulatory framework. The increasing number of marketing authorizations for biosimilars in recent years (over 52 MPs have been granted a marketing authorization since 2017) is clear evidence of producers' active pursuit of biosimilar development.
- This growing interest and pace of marketing authorization underlines the credibility of the regulatory framework's ability to ensure the safety and efficacy of these MPs. This regulatory framework's continuous development and improvement demonstrate the commitment to keeping up-to-date with advances in biotechnology and ensuring that patients have access to high-quality and affordable therapeutic options. The mentioned trend is commendable as it promotes competition and accessibility in the pharmaceutical industry, and over 70 biosimilar MPs are already on the market.

- **Lack of MPs with discontinued MA due to safety concerns:** Within the period from 04.2006 to 11.2022, 15 biosimilars were withdrawn, and 2 were not authorized. One notable observation was the absence of biosimilar MPs, which was the subject of rejected MA applications or withdrawals due to safety concerns. This claim underlines the EU's commitment to ensuring the protection of the well-being of patients. Implementing rigorous evaluation and monitoring procedures ensures that biosimilar MPs meet safety and efficacy standards. These measures promote competition and innovation in the biosimilar market, providing more affordable patient treatment options. In addition, the EU's commitment to transparency and information sharing further enhances trust in the safety and efficacy of biosimilar MPs among healthcare professionals and patients.

- **Equity in the additional monitoring of biosimilar MPs:** Using the same methods to further monitor the pharmacovigilance of biosimilar MPs as for reference products shows a commitment to monitoring them after MA and reducing the risks of harm. At the time of the study, more biosimilar MPs (n=40) are subject to additional monitoring compared to reference products (n=1). This statement highlights the EU's commitment to conducting comprehensive safety assessments of these products at every stage.

- **Transparency challenges and the need for improvements:** While remarkable progress has been made in strengthening the safety of biosimilar MPs, challenges remain related to the transparency and comprehensibility of publicly available information. The availability of comprehensive and comprehensible safety data relating to references and biosimilars is crucial to facilitating informed decisions by healthcare professionals and patients. Without access to transparent and easy-to-understand safety data, healthcare professionals may find it difficult to prescribe biosimilar MPs to their patients confidently.

- In addition, physicians and patients may be hesitant to switch from reference products to biosimilars without clear information on their safety profiles. Increasing transparency in the disclosure of safety data is imperative to promote trust in using biosimilar MPs within the health community. The EU must continue improving the accessibility and comprehensibility of safety-related information.

- **Standardization of Safety Information:** Analyses of the present work showed no significant differences in the safety information exhibited in the EPARs and RMPs for the selected INNs between reference products and biosimilars. The results suggest that regulatory

authorities prioritize the consistency and coherence of safety-related information for reference products and biosimilars. This is also confirmed by the forthcoming changes in legislation under which the RMP requirement for biosimilar MPs will be dropped.

- **Similarities in individual case reporting standards for ADRs:** Minimal differences were observed in the individual case reporting of ADRs to the EV for reference products and biosimilars. The majority of reaction groups showed minor deviations falling in the range of 0 to ±10%. This means that both product categories adhere to comparable strict criteria regarding disclosure of safety information. This sequence in reporting standards allows healthcare professionals and regulatory authorities to accurately assess the safety profiles of reference products and biosimilars. It also ensures that patients receive reliable and comprehensive information about potential side effects, allowing them to make well-informed treatment choices.
- **Focus on PASS:** The dissertation highlighted the proactive position taken by the MAHs in creating rigorous PASSs to ensure the continued safety of reference products and biosimilars. 95 PASSs were registered for the analyzed products as of 11.2022. The mentioned studies mainly use an observational methodology, emphasizing the commitment to continuous safety monitoring over an extended period. This approach allows the identification of various potential safety concerns that may arise once a drug is authorized. By closely monitoring the safety of references and biosimilars, MAHs can provide healthcare professionals and patients with accurate and up-to-date information to support informed decisions about drug choices. In addition, the observational methodology used in these studies helps collect data and assess the long-term safety profile of drugs in a diverse patient population.

In short, the comprehensive review of the safety profiles of biosimilars in the EU explains a regulatory framework that puts the protection of patient's well-being first while promoting competition and improving accessibility through the use of biosimilars. The results underline the EU's commitment to improving regulatory procedures, promoting transparency, and ensuring the safety and efficacy of biosimilars as a viable therapeutic choice for patients needing life-saving therapies. This work contributes significantly to the ongoing discourse on developing and regulating biosimilars, ultimately benefiting health systems and patients across the EU.

5.2. Recommendations

The review and comparison of biosimilars with their respective reference products have led to significant findings that can guide the various stakeholders involved in health decision-making. The following recommendations are designed to improve the use of biosimilars, protect patients' well-being, and promote well-informed decisions about treatment options:

1. To the EMA and the national competent authorities:

- **Improving and simplifying the legislative framework:** It is essential to continue the efforts to improve and simplify the legislative framework related to biosimilars. Facilitating the approval procedure by simplifying and optimising processes and rules has the potential to stimulate more pharmaceutical companies to engage in the development of biosimilars**.**
- **Promoting global harmonization:** There is a need for international cooperation and harmonization of rules and measures relating to biosimilars worldwide. Implementing a joint strategy can effectively reduce the regulatory barriers manufacturers face, thus simplifying the process of bringing biosimilars into the market.
- **Improving overall transparency:** Increasing safety-related information transparency for reference products and biosimilars. It is essential to ensure that healthcare professionals and patients are provided with easily understandable and unambiguous information through information guides and other types of material to facilitate informed decision-making.
- **Transparency in EudraVigilance:** The aim is to improve the transparency and comprehensibility of the information provided on the EudraVigilance website. The provision of a user-friendly interface that offers easily accessible safety data can enhance healthcare stakeholders' ability to adequately monitor and assess the safety profiles of reference and biosimilars.
- **Regular safety updates:** It is recommended that the regulatory authorities consistently provide regular safety updates to healthcare professionals and patients. This can be done by providing brief overviews of adverse event reports, changes in safety profiles, and any measures taken to reduce safety concerns in biosimilars.
- **Promoting interchangeability:** Continuation of efforts to promote interchangeability between reference products and biosimilars.

2. To the health insurance funds:

- **Evaluation and inclusion of biosimilars:** It is essential to continue evaluating and including biosimilars as equivalent alternatives within health insurance. Establishing an equivalent reimbursement for biosimilars, in line with reference products, can widen the range of available treatment options and promote the development of cost-effective health interventions.

3. To marketing authorization holders:

- **Progress of real-world data studies:** The promotion and financial support of research that uses real-world data to compare the safety and efficacy of biosimilar and reference MPs. These data have the potential to offer significant insight into the efficacy and safety of biologics in different patient populations and clinical contexts.
- **Advanced safety data:** Promote the deployment of comprehensive safety assessments for biosimilars by manufacturers covering extended study periods. These studies can potentially provide valuable data on the long-term safety profiles of biosimilars, thereby increasing the confidence level in their use.
- **Improving the training of healthcare professionals:** Deploying inclusive educational initiatives aimed at healthcare professionals, including doctors, nurses, and pharmacists, to increase their knowledge of biosimilars, including their safety profiles and the intricacies of interchangeability procedures.
- **Educating patients:** Creating educational materials and campaigns with a patient-centered approach to disseminate information about biosimilars, including their safety profile and the potential benefits of their use. This can enable patients to make well-informed decisions about their treatment.
- **Patient Advocacy:** Patient advocacy involves collaborating with patient support groups and advocacy organizations to increase knowledge about biosimilars and help patients consider these therapies.

4. To prescribers:

- **Gaining knowledge of biosimilars:** Prescribers are encouraged to acquire a proactive knowledge of the range of biosimilars already available, as well as relevant safety information for these products. Physicians must engage actively in acquiring knowledge of

biosimilars to be able to confidently prescribe these medicines, ensuring their suitability to meet the health needs of their patients. Educational and training programs can facilitate this process.

5. To the patients:

- **Encouraging active participation:** Patients are encouraged to learn about different treatment options, including biosimilars. They should actively engage in dialogues with their doctors about their prescribed courses of treatment. Conducting well-informed dialogues between patients and physicians can lead to treatment solutions that are better tailored and relevant to the individual patient's specific needs.

These guidelines underline the importance of promoting biosimilars' safe and affordable use and the need for joint efforts involving regulators, health insurance funds, pharmaceutical companies, doctors, and patients. Through collaborative efforts to improve regulatory processes, promote transparency, and provide patients and healthcare professionals with comprehensive knowledge, the healthcare ecosystem can effectively harness the potential of biosimilars. This use of biosimilars can lead to expanding treatment options, increased accessibility, and the maintenance of strict safety and efficacy standards. These initiatives align with the changing landscape of biopharmaceuticals and efforts to achieve better health outcomes for the entire population.

6. CONCLUSION

The advent of biosimilars has led to significant transformations in biotechnology and advanced medical care. The use of complex biologics represents a significant opportunity to improve patient access to vital therapies while positively impacting the long-term viability of health systems. Nevertheless, the deployment of biosimilars faces some obstacles, especially in ensuring their safety and building trust among healthcare professionals and patients.

One of the main challenges in implementing biosimilars is ensuring their safety and efficacy. Unlike generic medicines, which are exact copies of their reference products, biosimilars are highly similar but not identical to the reference biological product. This requires rigorous testing and regulatory oversight to ensure that they have comparable clinical outcomes and do not pose additional risks to patients. Furthermore, educating healthcare professionals and patients about biosimilars' benefits and potential risks is critical to building trust and promoting their widespread dissemination.

This dissertation undertook detailed research, entering the complex field of biosimilars, their regulatory framework, and their safety profiles.

The main objective of our undertaking was to establish a link between the theoretical foundations of the safety of biosimilars and the practical challenges faced by patients, healthcare professionals, and regulatory authorities.

Culminating in this endeavor, it becomes evident that our study has led to essential revelations and theoretical advances that have significant implications for biopharmaceuticals, regulatory science, and patient-centered care delivery.

These analyses and results can shape future policies and guidelines for the safety of biosimilars, ensuring that patients receive the highest standard of care. In addition, they stress the importance of cooperation between stakeholders to address the practical challenges they face in deploying biosimilars in health systems worldwide.

Our research was built on a comprehensive review of the regulatory framework for biosimilars in the EU since 2005. The importance of these analyses and results is to increase our theoretical understanding of biosimilars' evaluation and approval processes. The comprehensive

analysis of biosimilars approved, rejected, or withdrawn from 04.2006 to 11.2022 and the status of additional monitoring have shown distinct trends that will inform upcoming regulatory decisions.

The dissertation provided theoretical perspectives on the complexity and challenges of evaluating biosimilars with significant value in the dynamic biopharmaceutical field. In addition, the dissertation emphasizes the importance of continuous research and development in biosimilars to ensure their safety and efficacy. This knowledge will be crucial in shaping future regulatory frameworks and guidelines for approving biosimilars, benefiting patients and health systems worldwide.

Pharmacovigilance monitoring, a fundamental aspect of ensuring patient safety, is an area where our research has significantly improved theoretical frameworks. By carefully looking at the information in the EPARs, RMPs, and ADRs registered in EV and PASS, it was possible to understand biosimilars' safety profiles better. Our research has also highlighted the importance of real-world data to assess the safety and effectiveness of medicines, leading to more informed decision-making by healthcare professionals and regulators. By continually improving pharmacovigilance monitoring, we strive to contribute to improving patient care and advancing global health systems.

The concept of patient-centered safety and transparency is critical to healthcare delivery. It stresses the need to prioritize treating patients' well-being and inclusion in decision-making processes. The dissertation stresses the theoretical need for increased transparency of safety data. In order to increase patient confidence, healthcare professionals and patients must be provided with easily accessible, understandable, and transparent safety information on biosimilars and reference products.

This transparency can help patients make informed decisions about their treatment options and understand different medicines' potential risks and benefits. In addition, by ensuring that safety data are easily accessible and understandable, healthcare professionals can better identify potential problems or adverse events and take appropriate measures to reduce them, ultimately improving patient outcomes.

Completing this dissertation was instructive and transformative, effectively integrating academic foundations with practical application. However, it is necessary to note that this is not a final result but rather a significant achievement in the continuous pursuit of achieving the highest safety standards of biosimilars. The theoretical insights and contributions presented in this study require practical application. In pursuit of this goal, we provide recommendations from our theoretical findings and point the way to progress. In addition, it is crucial to invest in comprehensive training programs for healthcare professionals to increase their understanding and use of biosimilars, ultimately improving patient accessibility.

In summary, our research into the safety of biosimilars has shed light on the direction to be taken in the future. The theoretical foundations that have been established extend beyond this dissertation and have practical relevance to real-world decision-making, with potential implications for multiple people.

By acquiring new knowledge, we are gradually moving closer to an environment for biosimilars characterized by increased safety, improved accessibility, and a greater focus on patient needs.

In light of continuous developments in the biopharmaceutical field, it is crucial to maintain our commitment to achieving the highest safety standards for biosimilars. This commitment is critical to patients' effective therapeutic options, health systems' effectiveness, and society's general well-being.

7. CONTRIBUTIONS

7.1. Scientific and theoretical contributions

- Development of the regulatory framework: The dissertation paper provides a theoretical understanding of the dynamic development of the regulatory framework for biosimilars in the EU and Bulgaria since 2005. This contributes to the theoretical foundations of regulatory science by shedding light on the continuous improvement of guidelines, standards, and practices in the field of authorization of medicines in the EU.
- Life cycle analysis of biosimilars: The study offers a new theoretical input by extensively analyzing approved, rejected, and withdrawn biosimilars from 04.2006 to 11.2022. This theoretical framework has made it possible to understand and analyze the entire life cycle of biosimilars, including the reasons for approvals, rejections, and withdrawals that are directly relevant when used in patients.
- Concerning the comparative analysis of regulatory documents, the dissertation pioneered the theoretical approach, comprehensively comparing the EPARs and RMP summaries of the selected active substances as of 11.2022. This comparison analyzes the continuous improvement of the regulatory framework, highlighting compliance in reference and biosimilar MPs.
- Analysis of the reporting of suspected ADRs: The theoretical contribution of an extensive comparative analysis of ADRs reported to the EV for the selected active substances as of 11.2022 is fundamental, as it proves similarity in reporting ADRs and in quantitative terms. This theoretical framework deepens understanding of pharmacovigilance methodologies and highlights similarities and differences in ADR reporting in reference and biosimilar MPs, which may give physicians leeway in their application.
- PASS and Additional Monitoring: The dissertation expands the theoretical understanding of PASS by conducting a comprehensive analysis of these studies and products under additional monitoring as of 11.2022. This contribution highlights the critical role of post-marketing studies in assessing the long-term safety of biosimilars and their reference products once they are placed on the market.

7.2. Scientific and applied contributions

- Research in this dissertation highlights the need to improve the transparency of public information on the safety of references and biosimilars. This contribution highlights the importance of accessible and understandable safety information for healthcare professionals and patients.
- The work provides regulators and industry stakeholders with a solid basis for making informed decisions about the safety of biosimilars.
- Using real-world data, the dissertation proposes an approach to assess the safety profiles of biosimilars and reference products in actual clinical practice. This may provide further ideas and guidance for a follow-up study of the safety profiles of biosimilar MPs.

7.3. Confirmatory contributions

- The dissertation paper provided analysis and data on the comparability of the safety profiles of the selected biosimilar MPs with those of their respective reference MPs. This analysis serves as a basis for encouraging the interchangeability between reference and biosimilar MPs, which was also encouraged by the EMA and HMA through their joint opinion from 2023.

8. LIST OF PUBLICATIONS

- **List of full-text publications**

1. Kopanarov, V., Benisheva T. (2022). PHARMACOVIGILANCE OF REFERENCE AND BIOSIMILAR MEDICINAL PRODUCTS WITH INN – RITUXIMAB AND TRASTUZUMAB. "Man, Society, Medicine", Jubilee Scientific Conference, Proceedings. ISBN: 978-954-652-037-1
2. Kopanarov, V., Milkov, D., Naydenova-Tyunel, R.,Benisheva T. (2022). REGULATORY REQUIREMENTS FOR THE AUTHORISATION OF BIOSIMILARS. Health Policy and Management Journal, Vol. 22, No. 3, 2022 ISSN: 1313-4981
3. Benisheva, T., Milkov, D., Kopanarov, V., Ivanov, I., Dimitrov, D., Todorova, V., Dzhafer, N., Chavkova, I., Todorova, L. & Gebert, L. (2023) CONDUCTING CLINICAL TRIALS IN FIVE EASTERN EUROPEAN COUNTRIES (EU-EECS) WITH A FOCUS ON BULGARIA, Biotechnology & Biotechnological Equipment, 37:1. DOI: 10.1080/13102818.2023.2226741

- **List of posters published**

1. Kopanarov, V., Benisheva, T., Sidjimova, D., (2019). ADVERSE REACTION REPORTING IN THE EUROPEAN DATABASE EUDRAVIGILANCE – 2018 ANALYSIS. 3rd National Conference "Public Health – The capital of the future", Plovdiv, Bulgaria, 31st of May 2019. POSTER

- **List of presentations**

1. Kopanarov, V. (2019). PERIODIC SAFETY UPDATE REPORT (PSUR). Foundation Skills in Regulatory Affairs, Introduction in marketing authorization procedures, Market Access of medicinal products, Pharmacovigilance - One Day f2f Training Course,

Organized by Bulgarian Association for Drug Information (BADI), Sofia, Bulgaria, St. Ekaterina University Multiprofile Hospital for Active Treatment, 19th of April 2019. PRESENTATION

2. Kopanarov, V. (2019). MEDICINES UNDER ADDITIONAL MONITORING. Drug Regulatory Affairs – Update, Training Course 2019, Module II: Pharmacovigilance Part II, Organized by Bulgarian Association for Drug Information (BADI), Sofia, Bulgaria, Forum Hotel Sofia, 8th of November 2019. PRESENTATION
3. Kopanarov, V. (2020). GLOBAL REGULATORS MAP OUT DATA REQUIREMENTS FOR PHASE 1 COVID-19 VACCINE TRIALS. Regulatory News from EMA regarding COVID-19, Webinar organized by Bulgarian Association for Drug Information (BADI), Sofia, Bulgaria, 31st of March 2020. PRESENTATION
4. Kopanarov, V. (2020). OVERVIEW OF EMA MANAGEMENT BOARD MEETING. Regulatory News from EMA regarding COVID-19, Webinar organized by Bulgarian Association for Drug Information (BADI), Sofia, Bulgaria, 31st of March 2020. PRESENTATION
5. Kopanarov, V. (2020). COVID-19: HOW EMA FAST-TRACKS DEVELOPMENT SUPPORT AND APPROVAL OF MEDICINES AND VACCINES. Regulatory Update, Fourth Edition, Webinar organized by Bulgarian Association for Drug Information (BADI), Sofia, Bulgaria, 15th of May 2020. PRESENTATION
6. Kopanarov, V. (2020). PHARMACOVIGILANCE TRAINING MATERIALS. Drug Regulatory Affairs – Update, Training Course 2020, Module II: Pharmacovigilance Part II, Webinar organized by Bulgarian Association for Drug Information (BADI), Sofia, Bulgaria, 6th of November 2020. PRESENTATION
7. Kopanarov, V. (2021). PHARMACOVIGILANCE: PSUR. Foundation Skills in Drug Regulatory Affairs, Training Course organized by Bulgarian Association for Drug Information (BADI), Sofia, Bulgaria, 30th of September 2021. PRESENTATION
8. Kopanarov, V. (2021). PHARMACOVIGILANCE: EUDRAVIGILANCE. Foundation Skills in Drug Regulatory Affairs, Training Course organized by Bulgarian Association for Drug Information (BADI), Sofia, Bulgaria, 30th of September 2021. PRESENTATION
9. Kopanarov, V. (2021). POST-AUTHORIZATION SAFETY STUDIES (PASS) OVERVIEW. Pharmacovigilance, Pharmacoepidemiology – Regulatory Update, Training

Course 2021, Module I organized by Bulgarian Association for Drug Information (BADI), Sofia, Bulgaria, 8th of October 2021. PRESENTATION

10. Kopanarov, V. (2021). BIOSIMILARS AND DRUG SAFETY. Pharmacovigilance, Pharmacoepidemiology – from Regulatory Practice, Training Course 2021, Module II organized by Bulgarian Association for Drug Information (BADI), Sofia, Bulgaria, 5th of November 2021. PRESENTATION
11. Kopanarov, V. (2022). PHARMACOVIGILANCE: PSUR. Foundation Skills in Drug Regulatory Affairs, Training Course organized by Bulgarian Association for Drug Information (BADI), Sofia, Bulgaria, 13th of May 2022. PRESENTATION
12. Kopanarov, V. (2022). PHARMACOVIGILANCE: EUDRAVIGILANCE. Foundation Skills in Drug Regulatory Affairs, Training Course organized by Bulgarian Association for Drug Information (BADI), Sofia, Bulgaria, 13th of May 2022. PRESENTATION
13. Kopanarov, V. (2022). PHARMACOVIGILANCE INSPECTIONS & AUDITS: ONLINE CHALLANGES. DRUG REGULATORY AFFAIRS – update, Training Course, MODULE 1 - Pharmacovigilance - Regulatory Update, Part I organized by Bulgarian Association for Drug Information (BADI), Sofia, Bulgaria, 7th of October 2022. PRESENTATION
14. Kopanarov, V. (2023). PHARMACOVIGILANCE INSPECTIONS & AUDITS: REMOTE/HYBRID CHALLANGES. DRUG REGULATORY AFFAIRS – update, Training Course, MODULE 1 - Pharmacovigilance – Update organized by Bulgarian Association for Drug Information (BADI), Sofia, Bulgaria, 6th of October 2023. PRESENTATION