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PHARMACEUTICAL MANUFACTURERS ASSOCIATION OF TURKEY

Biotechnological Drugs

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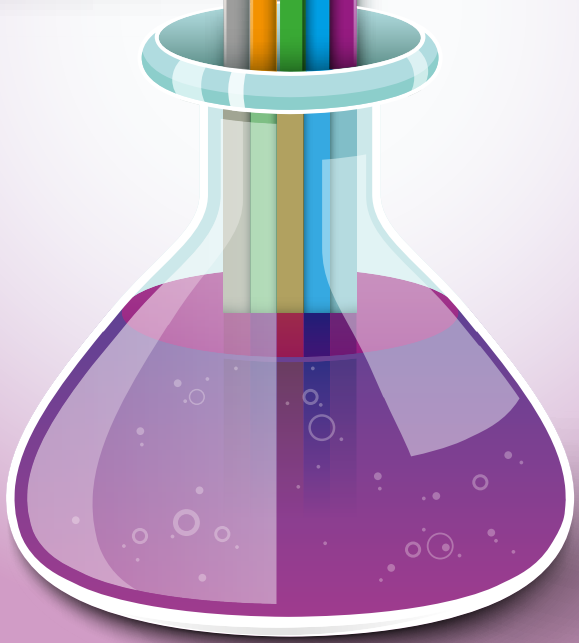
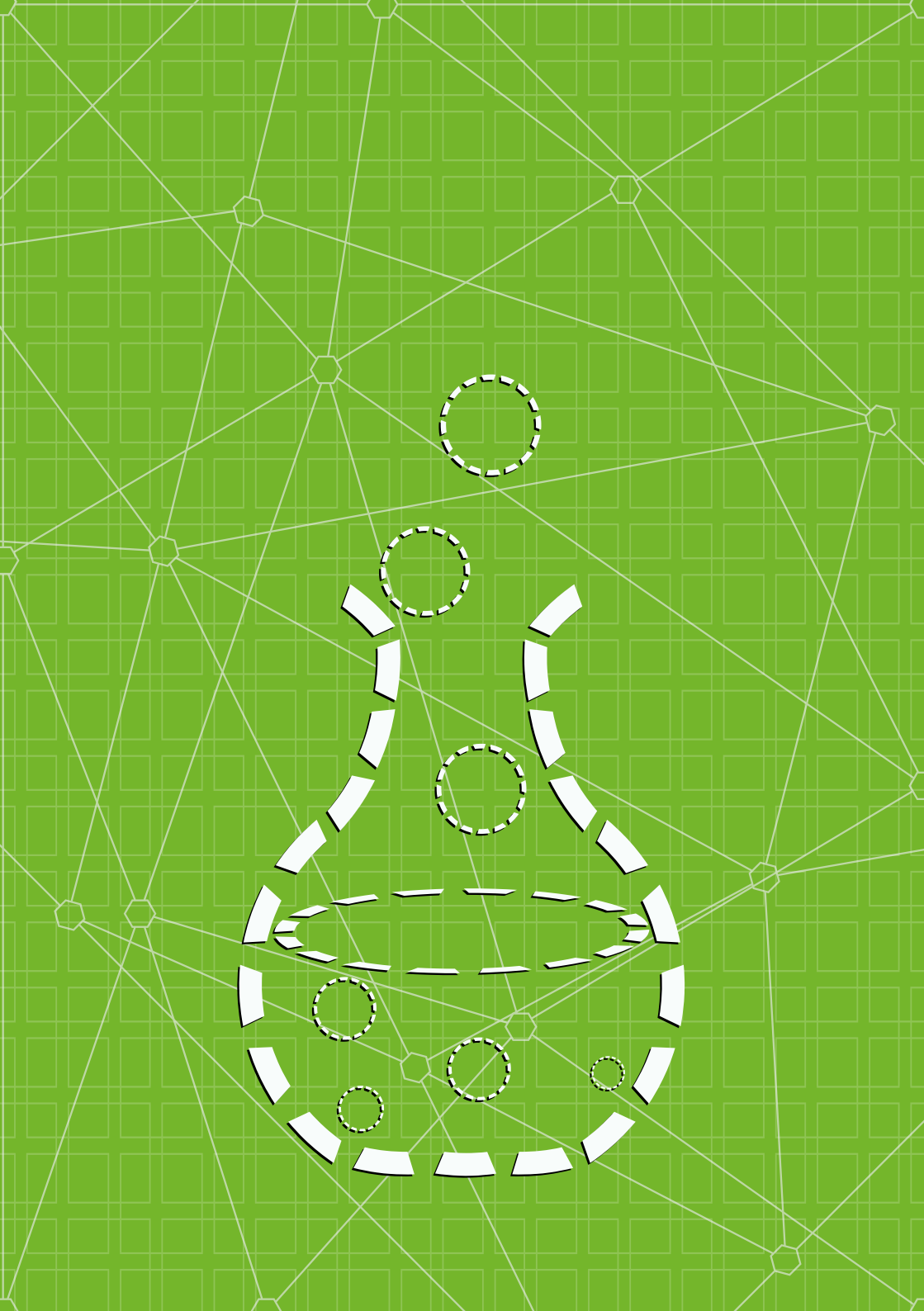




Introduction

Biotechnology has a key importance for the pharmaceutical industry to advance so as to serve to human health. Given recent conditions, only 10,000 of the approximately 30,000 known diseases can be treated. Biotechnological methods have been increasingly more effective than chemical and herbal formulations in the development of new drugs.

The ratio of the biotechnological drugs in the newly licensed drugs has been increasing in recent years. Major part of the new drugs developed for the treatment of 200 diseases including cancer, alzheimer, heart diseases, diabetes and rheumatoid arthritis consists of biotechnological drugs.

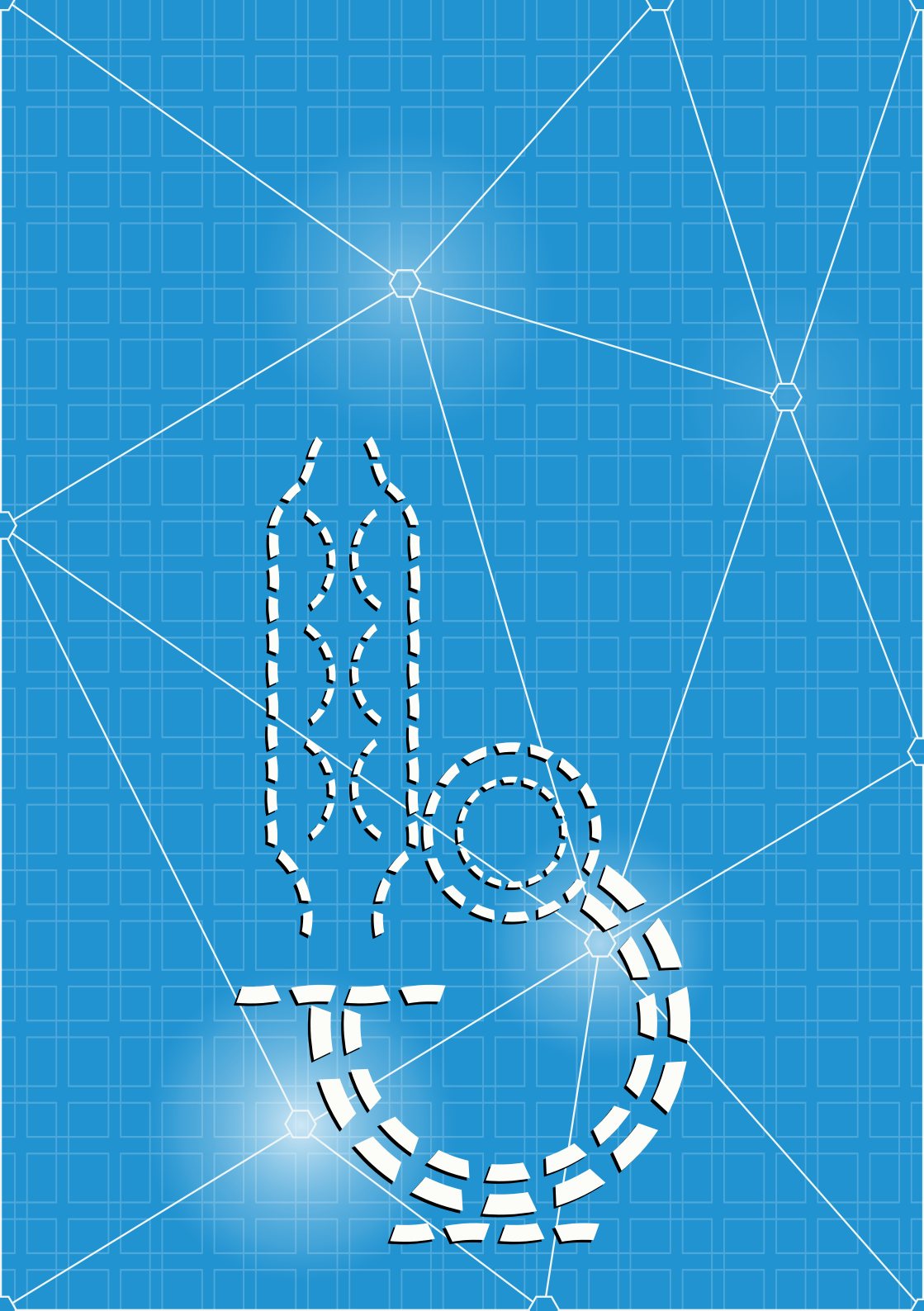
Biotechnological products making a breakthrough in human health are expensive products due to their high production and development costs.

Biosimilars increase the access of the patients to biotechnological drugs while decrease the costs by creating competition and contribute to the financial sustainability of the health system. In addition, putting biosimilars up for sale offers new treatment options for physicians and patients.

The differences between the national health systems, structures and processes of EU countries affect the penetration of the biosimilars. Turkey is one of the important centers for the global pharmaceutical industry. However, only some stages of the production of biosimilar products can be carried out and most part of the biotechnological products are imported in our country. Turkey pays an average of 1 million dollars per kilogram of biotechnological drugs. With the increase of the share of biotechnological drugs in the global pharma market, an import-dependent biotechnological drug supply model is not sustainable for Turkey, and it is clear that the current account deficit of Turkey in the area of pharmaceuticals will increase unless it is supported with domestic production.

All stages of the biosimilar product manufacturing can be realized in our country. Domestic production of these products is very important in terms of;

1- Establishment of this expensive technology in our country,
2- Accelerating the access of patients to biotechnological products,
3- Offering different alternatives to physicians,
4- Narrowing down the foreign trade deficit due to drug import,
5- Utilizing the public health budgets more efficiently by dragging the prices of the products down with the new product range to be obtained by the penetration of new products into the market,
6- The prospective competition environment to be created to direct the researcher companies to find more innovative drugs.



Biotechnological Drugs in Turkey

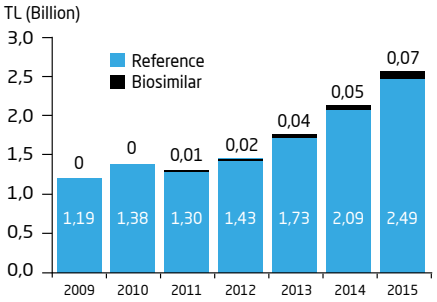
There are 183 reference biotechnological and 38 biosimilar drugs in Turkish market. 13 (34%) of the biosimilars are produced in our country. As for the share biotechnological drugs among the prescription drugs is standing at the level of 17% in 2015.

When we examine the reference biotechnological drug market; the market which was 2.09 billion TL in 2014 reached 2.5 billion TL in 2015 with a growth of 19.4%. The share of these drugs in the prescription drug market reached 16.6% in 2015.

The biosimilar products containing abciximab, enoxaparin sodium, epoetin alfa, erythropoietin, erythropoietin alfa, filgrastim, infliximab and somatropin were licensed in Turkey. The drugs containing enoxaparin sodium, epoetin alfa, infliximab are produced in Turkey. The number of the biosimilar products is expected to increase rapidly in the forthcoming period as a result of the expiration of the reference biotechnological drug patents.

When we examine the biosimilars market; it is seen that it reached 73.6 million TL in 2015 with an increase of 59.3%.

Biotechnological Products (Value)



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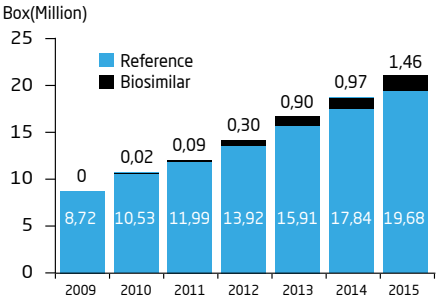
Biotechnological Products (Volume)



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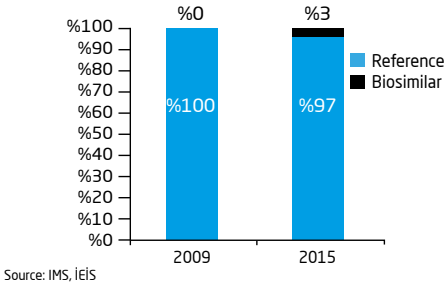
Biosimilars had almost no share in biotechnological drugs in 2009 while they had 3% in value and 7% in volume in 2015.

Reference - Biosimilar Products Market Share (Value)



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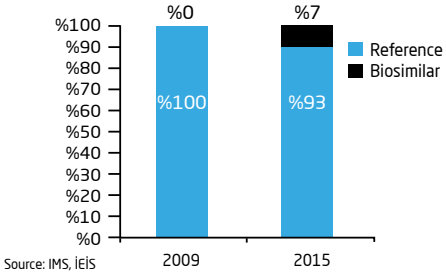
Reference - Biosimilar Products Market Share (Volume)



Source: IMS, İEİS

Once they were classified on basis of ATC 2 group, it is seen that biotechnological products significally increased the share of antianemic preparations and antithrombotic drugs within biosimilar products in 6 years. On the other hand, in the reference biotechnological drugs market, immunomodulatory agents, insulins and their analogues take the lead. Insulins and their analogues and antineoplastic drugs have a share of 26% and 10% respectively in reference biotechnological products while these groups are not presently available in biosimilar products.

ATC 2 Breakthrough of Biotechnological Drugs	Box		Value	
	2009	2015	2009	2015
Biosimilar	**%100**	**%100**	**%100**	**%100**
Antianemic Preparations	%0	%14	%0	%39
Antithrombotic Drugs	%0	%75	%0	%27
Immunomodulator Agents	%100	%8	%100	%22
Pituitary, Hypothalamic Hormones and Analogues	%0	%4	%0	%12
Reference	**%100**	**%100**	**%100**	**%100**
Immunomodulator Agents	%8	%7	%34	%32
Insulins and analogues'	%62	%61	%25	%26
Antineoplastic drugs	%2	%1	%15	%10
Ophthalmologics	%0	%1	%1	%7
Digestive System and Metabolism Products	%0	%0	%2	%5
Vitamin K and Other Hemostatics	%0	%1	%1	%5
Antianemic Preparations	%4	%2	%10	%3
Antithrombotic Drugs	%17	%20	%3	%3
Sex Hormones and Genital System Modulators	%2	%2	%4	%3
Pituitary, Hypothalamic Hormones and Analogues	%3	%4	%4	%3
Other Systemic Drugs Used in Obstructive Respiratory Disease	%0	%0	%0	%2
Immune Serums and Immunoglobulins	%0	%0	%1	%1

Development of Biosimilars

Biotechnological drugs have larger molecules than conventional drugs and each has a number of properties that vary in nature at a certain level. This variability can be the type and length of any sugar or carbohydrate (glycolysis) that may be molecularly added by the 'shape' (folding) of the molecule.

Biotechnological drugs are produced by using living organisms. The production process is complex and requires advanced technology since the biologically active substance which is the final product inside the living cell or organisms must be separated and purified from thousands of other molecules.

Standard production flow of biotechnological drug

Development stages of biosimilars

Step 1: (1-1,5 years)
Development of the equivalent host cell clone

Step 2:
Preparation of cell bank clones

Step 3: (1-1,5 years)
Process Development • Fermentation • Purification

Step 4:
Expansion of manufacturing scale

Step 5: (3,5 - 4,5 years)
Comparability Tests • Analytics • Characterization

Comparability

The comparability of reference biotechnological and biosimilar products is the fundamental principle of drug development. Comparability analyses are based on the one-to-one comparison of the reference biotechnological and biosimilar products in terms of quality, reliability and efficiency levels.

The development of biosimilars requires comparability testing at all levels, i.e. quality, non-clinical and clinical development stages, in addition to extensive product and process development studies. Therefore, throughout all drug development programs, the same reference product is used during biosimilar product comparability studies.

The comparability study is a complicated and difficult study. However, now we have highly sophisticated analytical methods and validation tools that allow for detailed characterization of these products.

Step by Step Comparability Studies

1. Step — Comparability of Quality (Physicochemical and Biological Comparability)

A meticulous characterization program must be performed to compare the physicochemical and biological quality characteristics of biosimilars including purity with the reference product. Since all aspects of a product cannot be characterized by a single method, this characterization is performed using a series of tests consisting of modern analytical tests.

When significant differences are detected in the analysis, the product development process is continued based on all the criteria that the regulatory authority deems necessary at each stage of the development process, until the final biosimilar drug profile coincides with the profile of the final reference drug.

2. Step — Nonclinical Comparability (Comparative Nonclinical Studies)

The nonclinical data for a biosimilar are generally produced from the shortened programs of the in vitro tests or animal studies as required by the regulatory authority.

Nonclinical studies generally consist of local tolerance tests and pharmacokinetic and pharmacodynamic (PK/PD) studies in a suitable animal model as well as repetitive dose toxicity studies.

In order to support the comparability of the biosimilar and reference products, the PK/PD measures of these studies and predefined similarity levels must be scientifically proven.

The aim of these studies is to support the comparability more or to detect the potential differences between biosimilar and reference products.

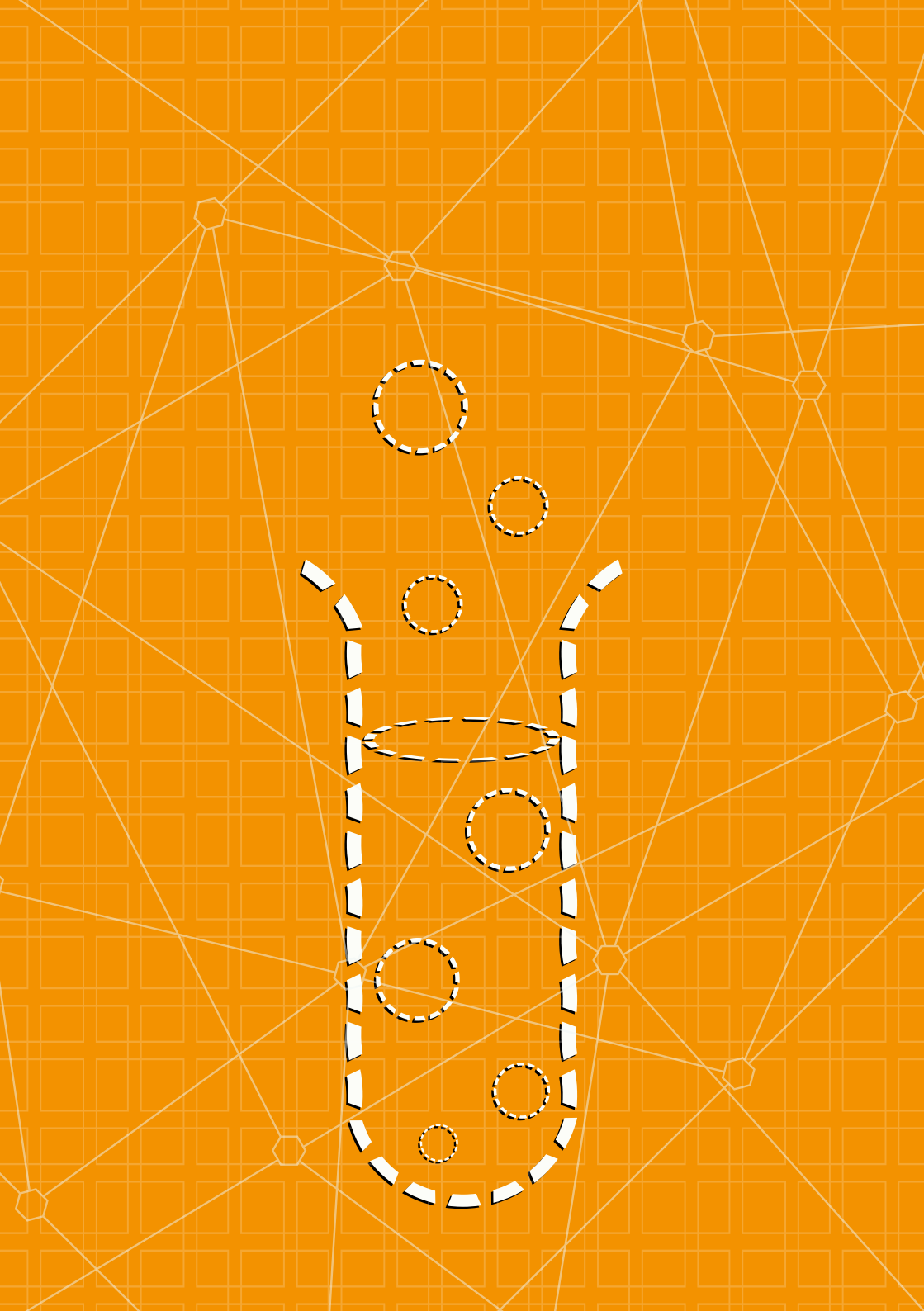
3. Step Clinical Comparability (Comparative Clinical Studies)

Due to the clinical experience obtained from the usage of reference product for many years, the clinical testing of a biosimilar does not need to be comprehensive as required for a new active agent. Therefore, the similarity level of the drug profile with reference product and the nature, qualifications and intended purposes of the drug must be taken into consideration when designing clinical development program in coordination with regulatory authority and scientific committee. The closer the structural profiles of the biosimilar and reference products and the greater the similarity of the functional characteristics provided it is shown by appropriate quality, biological and receptor binding/separating tests, animal tests, and etc. it is more likely that the regulatory authority and scientific committees to approve a narrow-scoped clinical development program.

Thus, unnecessary human tests and the increase in the drug costs caused by unnecessary development expenses are preventable with the development of the clinical researches at a sufficient extent.

Clinical comparability studies generally start with PK and/or PD researches. At the next stage or within more indications, the comparability clinical efficiency and reliability studies are conducted. It must be shown that the reliability profile is also comparable in terms of the severity and frequency of the different undesired impacts in addition to the comparability of the efficiency. It is also a key component of clinical safety data analysis that the immunogenicity profiles of the biosimilar and the reference product is comparable and that this comparability is examined in an indication with a wide impact area and in sensitive patient group.

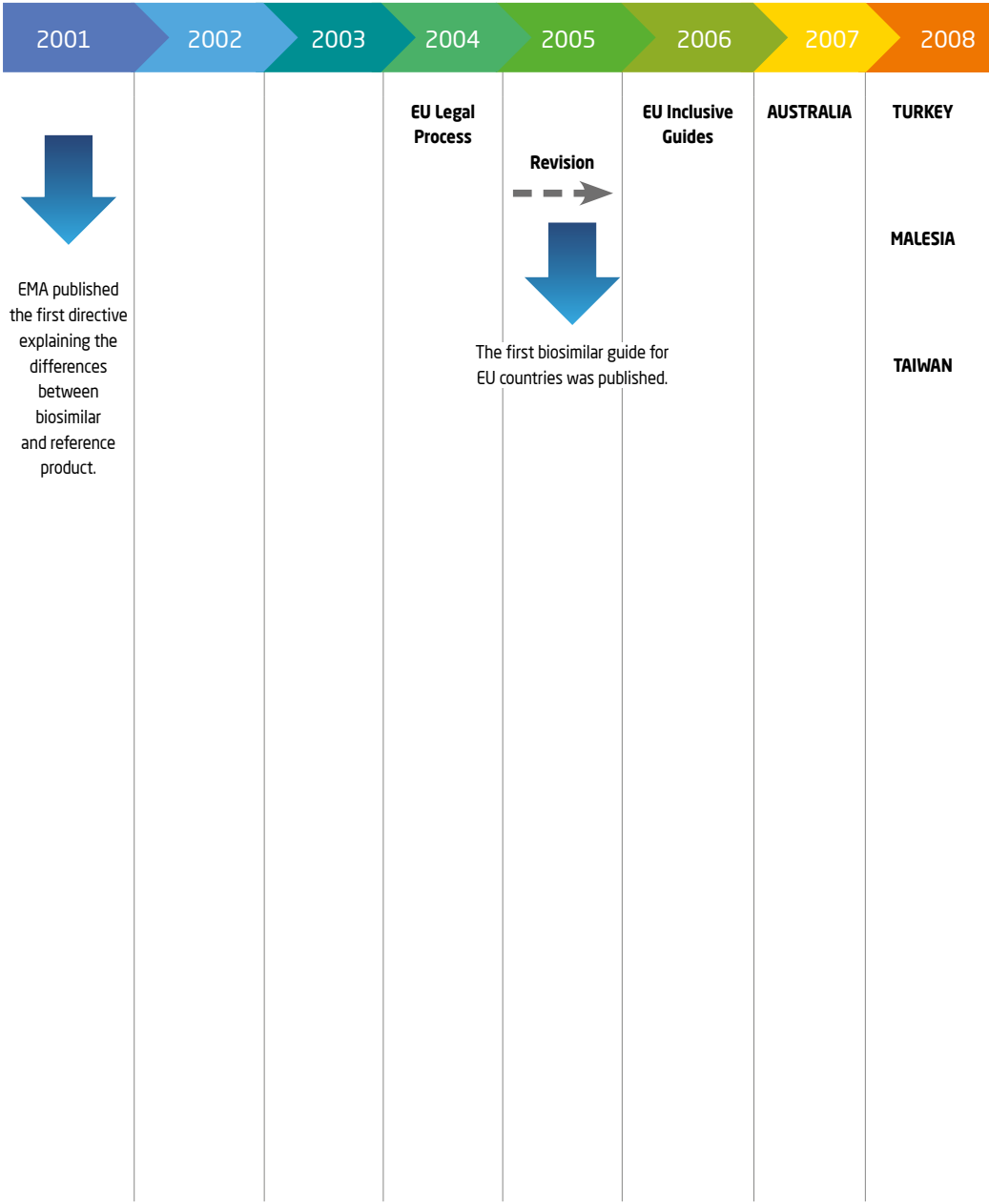
The primary aim of an investigation on a biosimilar is not to define the benefit/risk profile from the beginning but to evaluate the comparability with the reference product qualitatively and quantitatively.



Regulations on Biosimilars

With the increase of biosimilars worldwide, The World Health Organization (WHO) set standards on the reliability, efficiency and quality of biosimilars in 2009 in order to assist the guides constituted by the local authorities. Since then, country regulations within the scope of the general criteria set by WHO showed a rapid increase.

Global Biosimilar Guides



2009	2010	2011	2012	2013	2014	2015
SOUTH KOREA	**CANADA**	**ARGENTINA**	**USA** (Draft)	**EU** Updated Guides	**FRANCE** (Substitution at pharmacy)	**USA** FDA Guide
JAPAN	**SOUTH AFRICA**	**MEXICO**	**COLOMBIA** (Draft)	**EU** Nonclinical and clinical guides were renewed.	**USA** Substitution at pharmacy in 8 states (Massachusetts, Florida, Virginia, Delaware, Indiana, Utah, North Dakota and Oregon)	**USA** FDA Guide
SINGAPORE	**BRAZIL**	**CUBA**	**TAYLAND** (Draft)			**CHINA** (Draft)
WORLD HEALTH ORGANIZATION	**SAUDI ARABIA**	**IRELAND**	**EU** Quality guide was revised			**AUSTRALIA** Nonclinical and clinical guides were renewed.
	NORWAY The first biosimilar product was added into the substitution list.	**INDIA**				**AUSTRALIA** (Substitution at pharmacy)
		PERU				**JORDAN**

The European Medicines Agency (EMA) published the first biosimilar guide in 2005 and licensed the first biosimilar in 2006 and then licensed the 16 biosimilar products with the groups given below until 2013.

- Recombinant erythropoietins (epoetin alfa, epoetin zeta)
- Recombinant granulocyte - colony stimulating factors (filgrastim)
- Recombinant growth factor (somatropin)
- Recombinant follicle stimulating hormone (follitropin alfa)
- Monoclonal antibodies (infliximab)

Different terms used for "biosimilar" concept

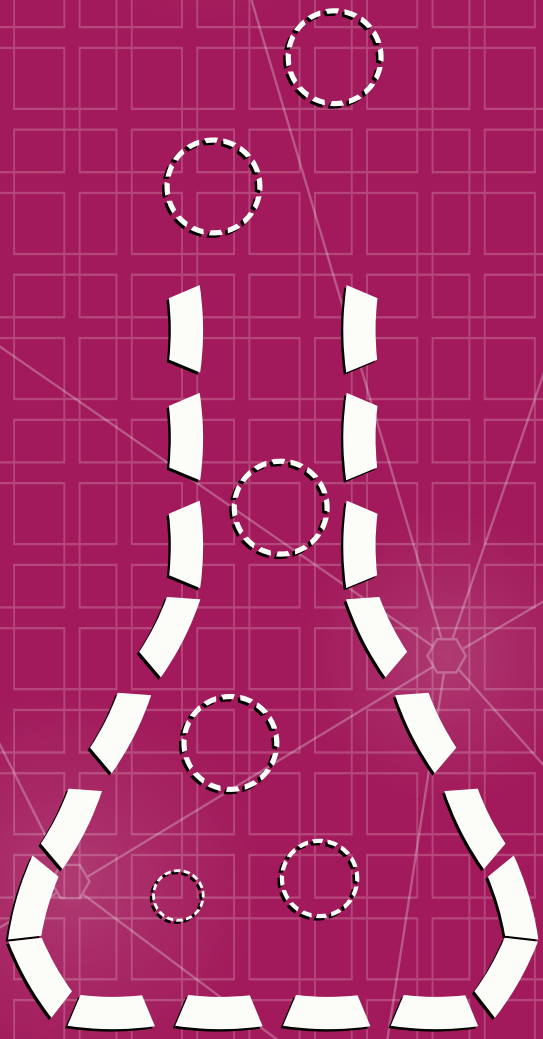
Authority	Term	Definition
WHO	Similar biotherapeutic products	Biopharmaceutical product similar to the reference biopharmaceutical product previously licensed in terms of quality, safety and efficiency
Japan	Following proteins or following biotechnological products	Product clinically having no significant differences in safety, purity and potency and is very similar to the reference product
Canada	Subsequent biotechnological products Biosimilars	Biotechnological product if which the similarity with the version previously licensed in Canada was shown
EMA, WHO, South Korea, India, China, Australia		Biotechnological products of which the equivalency with approved reference product in terms of quality, reliability and efficiency was shown

The common point of all the guides published worldwide is the necessity of the proof of the similarity of the reference biotechnological product with its biosimilar in terms of quality, nonclinical and clinical aspects with reliable data. Authorities published guides in line with the territorial requirements by prioritizing the product reliability and efficiency.

The contents and differences of the sample guidelines published and implemented by countries

Authority	Scope	Reference Product	Pharmaco-kinetic (PK)
 **WHO**	It includes well-formed and well-characterized therapeutic proteins developed by recombinant DNA technology.	The manufacturer of the similar biopharmaceutical product should justify the selection of the reference biotechnological product for local license application.	PK studies must always be examined. PK studies must be comparative.
 **EU**	It includes any biotechnological medical product, e.g. the products with active agent produced biotechnologically or vaccines, blood products, immunological products such as monoclonal antibodies, the products that are most likely and highly purified and well-characterized.	The selected reference medical product used in the license applications to the union must be used during the development phase of a similar biotechnological medical product.	The comparative PK studies are the fundamental part of the comparability studies.
 **Japan**	It includes recombinant proteins and polypeptides, their derivatives and the structures of which these products are components. These proteins and polypeptides were produced from the recombinant expression systems consisting of microorganisms or cell culture, and they can be purified at high level and well-characterized with appropriate analytical methods.	The reference product must be certified in Japan and must be the same as that used in the development period of the biosimilar product.	The biosimilar manufacturer must conduct comparative PK study.
 **South Korea**	It includes all biotechnological products. It especially includes the biotechnological products containing well-characterized proteins.	The reference medical product must be certified in Korea. However, if the reference product is not included in health area or has another justifiable reason, it can be purchased from the countries outside Korea and can be used as reference product.	PK studies must always be examined. PK studies must be comparative.
 **Canada**	It includes the biotechnological products containing all the well-characterized proteins that are produced by using modern biotechnological methods such as recombinant DNA and/or cell culture.	The reference biotechnological drug must be certified in Canada; must be presented in health area and used in studies. The product that is not certified in Canada for sale can also be used as reference product under appropriate conditions.	Comparative PK study must be conducted.

The products produced by biotechnological methods constitute a very wide range. Therefore, all the biotechnological products including the biosimilars in the EMA guide, also taken as example by our country, were classified based on their classes and an individual guide was prepared for each one (such as erythropoietin, monoclonal antibodies).



Main Topics on Biotechnological Drugs

Conventional Drugs	Biological Drugs
Produced by chemical synthesis	Produced biotechnologically
Low molecular weight	High molecular weight
Physicochemical properties are completely characterizable	Complex physicochemical properties
Stable	Sensitive to heat and agitation (aggregation)
Purity standards are available	Variable specifications
Dosage forms for different modes of administration can be prepared	Generally administered parenterally
Rapidly get into systematical circulation through blood vessels	Can reach systematic circulation through lymphatic system and be proteolized
Dispersed in organs and tissues	Dispersion limited with plasma and intercellular fluid
Generally specific toxicity	Receptor mediated toxicity
Generally non-antigenic	Generally antigenic
Complete characterization by analytical methods	Difficult characterization
Easily purified	Long and complex purification process
Easy to be protected against contamination	Very high contamination possibility

Assessment of Immunogenicity

The term "immunogenicity" defined as the immune response of the immune system to exogenous protein is the most important reliability criteria of all the biotechnological drugs including reference biotechnological and biosimilar drugs. Generally, biotechnological drugs can create immune response in the body due to their large and complex structures.

Authorities request the assessment of immunogenicity before licensing since it has a lethal risk although occurred in few cases.

Immunogenicity risks are assessed in small molecule chemical drugs by preclinical studies while it cannot be assessed in preclinical studies since the immune response in biotechnological drugs having a protein structure vary based on species. Therefore, a detailed assessment must be carried out and the immunogenicity must be included in risk management plans before licensing.

Immunogenicity is related to the following factors according to the EMA guide. Therefore, it is considered that taking these factors account for the monitoring of the product reliability in especially clinical phase studies will provide convenience.

The factors related to immunogenicity are listed below:

1. Patient and disease related factors

- Genetic factors affecting immune response
- Age
- Disease related factors
- Simultaneous treatment programs
- Treatment period, administration mode, treatment methods
- Previous exposure to similar or related protein

2. Product related factors

- Antigenic structure of protein
- Formulation
- Attachments formed outside the aggregation and protein structure
- Impurities
- Physicochemical interactions related to primer package
- Variables depending on storage conditions

Authority	Reliability (immunogenicity)
 WHO	Reliability data must be collected before licensing. The frequency and type of the induced antibodies and the potential clinical results of immune response must be compared.
 EMA	Reliability data must be collected before licensing. The immunogenicity of biosimilar medical product must always be investigated.
 Japan	The reliability studies including immunogenicity must be considered. Studies showing antibody formation and other immunogenicity factors must be conducted at an appropriate stage of clinical development.
 South Korea	Reliability data must be collected before licensing. The frequency and type of the induced antibodies and the potential clinical results of immune response must be compared.
 Canada	The nature, severity and frequency of adverse effects must be compared. The immunogenicity of biosimilar medical product must be investigated.

Pharmacovigilance and Risk Management

Monitoring the response of patients for all drugs and reporting their side effects are important for the safety and effectiveness of the treatment.

Pharmacovigilance and risk management plans should be established before biotechnological drugs break into the market, and continuous follow-up of the product should be performed during it is in clinical practice. The complex structure, multi-step and complex production method of the product and the fact that it has a biological origin and minor changes may be observed in each series of production should be kept in mind in the evaluation of biotechnological products reliability and development of pharmacovigilance system and risk management plans.

It is obvious that the safety and effectiveness of these products will only become clear after the product is used regularly on a daily basis. Therefore, the applicant firm should give special importance, gain operability to its pharmacovigilance system and follow up it for these products. Also, it is of great importance that the country's health authorities, health workers and patients follow up adverse event reporting encountered during the use of

all biotechnological products.

The pharmacovigilance plan should be based on the safety specification and recommend measures for safety issues identified. If there is no specific problem in small chemical products, it is sufficient to carry out only routine pharmacovigilance activity without any additional measure within the scope of post-registration safety monitoring studies. However, additional studies for biotechnological products must be carried out and followed up on a routine basis.

The Regulation on the Reliability of Drugs, published on 15 April 2014 in our country, contains a provision on the definition of biotechnological products. Accordingly, the regulatory authorities are responsible for securing that all biological products prescribed, supplied or sold to patients therefore having a potential of being subject to an adverse reaction are describable by gathering information continuously and if necessary following them.

The application of 'inverted black equilateral triangle' with at least 5 mm length on each side has also entered into force on 15 April 2014 in order to strengthen the follow-up of biotechnology products that are among the drugs subject to additional monitoring in our country. With the regulation reference biotechnological products having license applicaton after 15 April 2014 and all biosimilars and are subject to monitoring.

This application was put into practice in the EU in 2011 and started to be applied to all biotechnological drugs for which license application is made after 2011 without distinction of reference biotechnological and biosimilar.

In our country, it will be appropriate to observe the application with the inverse black equilateral triangle by further monitoring of all biotechnological drugs for which license application was made after 15 April 2014. Applying the application to all products will prevent any potential misperception and impression e.g. the drugs subject to additional monitoring are not safe.

Extrapolation of Indications

Biotechnological products are generally used for more than one indication. Their activity mechanisms for the treatment are often common in these various indications. Therefore, if it is demonstrated that the biosimilar drug has a clinical similarity with the reference product for an indication, this allows to expand the reliability and efficiency data to include other indications for which the drug has obtained approval.

This called as extrapolation. The scientific reason of extrapolation is that there is a proven, in-depth comparability between qualities of biosimilar and reference biotechnological products. An approved biosimilar is used with the same doses as the reference drug in the treatment of the same diseases.

INN

A common INN with a unique trade name is sufficient to provide the name of the manufacturer/licensee, national drug tracking system code and production serial number traceability. Although there have been biotechnological products with the same INN in Europe since 2006, this did not lead any problem related to traceability and drug safety. A biosimilar having the same INN with its reference builds up trust for physicians, pharmacists, patients and their relatives.

Within the framework of regulatory requirements, each biosimilar must either carry a trade name or its active substance name as well as the name of licensee company. In this way, it is possible to clearly describe each biosimilar product by referring and following with a unique name.

In the past, WHO has recommended to Member States to assign "biological qualifier: BQ) code (an affix with four consonants to the end of INN) for biosimilars based on the API. Such coding may meet the traceability and pharmacovigilance requirements in countries where the commercial name of drugs, their license holders, their national barcodes, serial and production numbers are not sufficiently taken into account. However, assigning different codes for all biotechnological drugs not only for similar drugs without discrimination and for each new production series will be an approach that will meet the actual need. The INN-BQ coding obsivously will make it difficult for physicians, pharmacists and patients to differentiate drugs. Therefore, it cannot be expected that the use of BQ as is, would provide an additional pharmacovigilance benefit, especially in markets such as Turkey and EMA.

The Pharmaceutical Track & Trace System that was first implemented in our country in the world in this context provides more detailed traceability of the drug with barcode, trade name, serial and batch number via data matrix. Then, it is not required to give a different INN.

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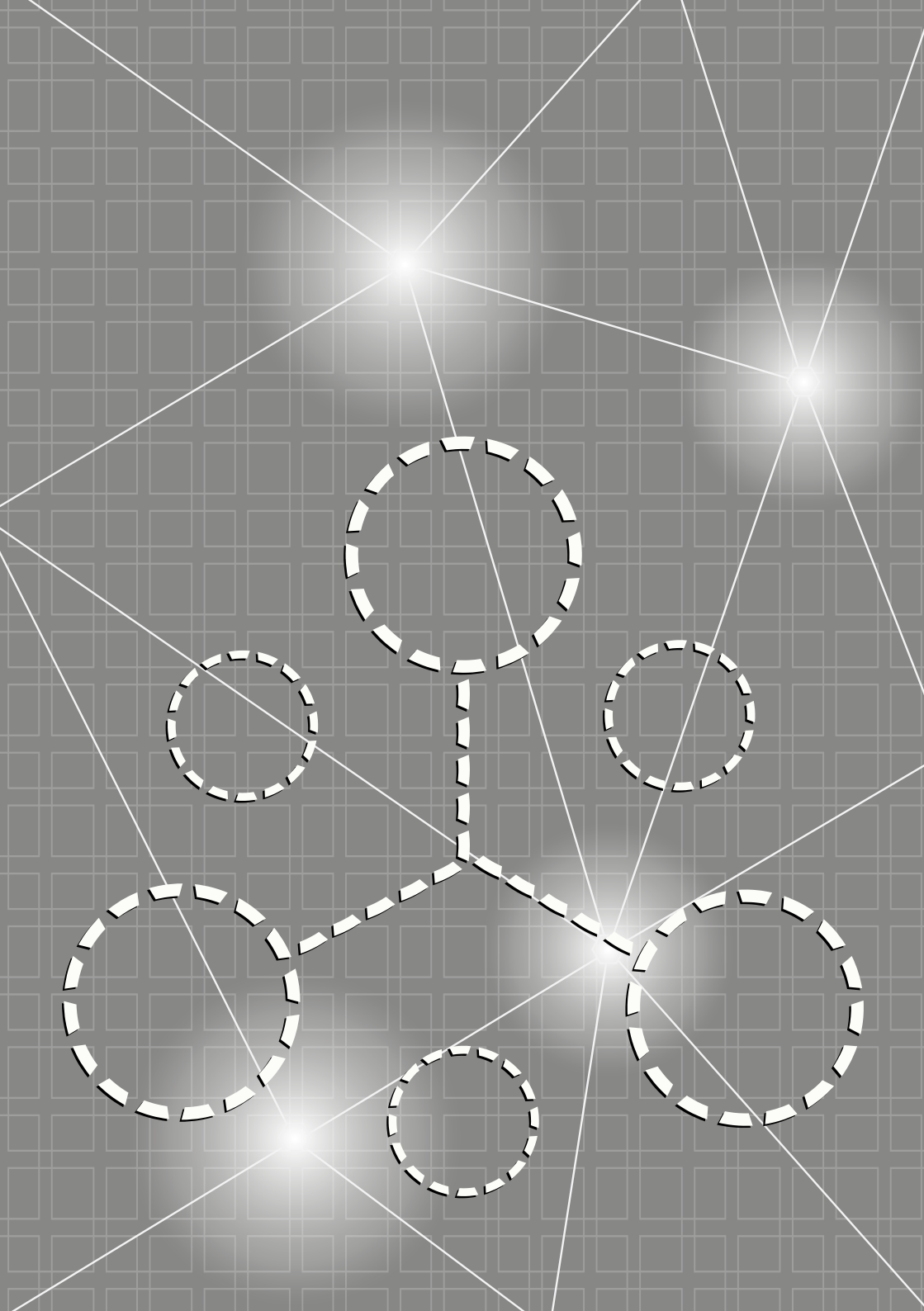
- American Food and Drug Administration (FDA)
- European Medicines Agency (EMA)



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