POSITION AND RECOMMENDATIONS OF THE INNOVATIVE PHARMACEUTICAL INDUSTRY ASSOCIATION (IFPA) REGARDING USAGE OF BIOLOGICAL MEDICINAL PRODUCTS

THE INNOVATIVE PHARMACEUTICAL INDUSTRY ASSOCIATION

Summary

By this document the Innovative Pharmaceutical Industry Association (IFPA) following recommendations of European Biopharmaceuticals Enterprises (EBE) and European Federation of Pharmaceutical Industries and Associations (EFPIA) points out its position and recommendations related to usage of all biological medicinal products taking into account that due to the complexity of biological / biotechnology-derived medicines, they cannot be regarded as generics and therefore, the approach used to deal with generic medicines is not scientifically appropriate for these products.

The IFPA acknowledges that similar biological preparations are important to healthcare system and to society. In addition, the IFPA recognizes the quality, safety and efficacy of biosimilars when they are authorized following requirements of legal acts of the European Union.

According to the opinion of the IFPA the automatic substitution is inappropriate for biologic medicines, including biosimilar medicines. The IFPA recommends that the decision regarding administration of particular biological medicinal product to individual patient or substitution of one biological preparation with another (independently if the preparation is original or biologically similar preparation) must always be made by treating physician. Therefore, the physician should retain decision-making autonomy and have unrestricted choice of products to prescribe.

The IFPA recommends following the requirement that all biological medicinal products, including biosimilar medicines, should be prescribed by indicating brand name and not only International Nonproprietary Name (INN) of medicinal product in order to facilitate compliance with the patient safety and Pharmacovigilance identification and traceability requirements.

The IFPA considers that patients have to be informed and take part in treatment decision before any change of medicinal product substituting medicinal products with one another.

Original biological medicinal products and similar biological medicinal products (biosimilar) general principles

Biological medicine- is a medicine whose active substance is made by a living organism and are usually large and complex molecules Biological medicines contain active substances from a biological source, such as living cells or organisms (human, animals and microorganisms such as bacteria or yeast) and are often produced by cutting-edge technology. European Medicine Agency (EMA) guidelines indicate that biosimilar is a biological medicine highly similar to another biological medicine already approved in the EU (the so-called 'reference medicine') but due to the natural variability of the biological source and to the manufacturing process unique to each manufacturer, minor differences can occur between the biosimilar and its reference medicine. Some degree of variability is inherent to all biological medicines and minor differences may occur among different batches of the same biological medicine. A biosimilar is not regarded as a generic of a biological medicine. This is mostly because the natural variability and more complex manufacturing of biological medicines do not allow an exact replication of the molecular microheterogeneity.

European Medicine Agency (EMA) recognizes complexity of molecules of biological medicinal products and indicates that due to the complexity of biological and biotechnology-derived products the standard generic approach (demonstration of bioequivalence with a reference medicinal product by appropriate bioavailability studies) which is applicable to most chemically-derived medicinal products, is in principle not sufficient to demonstrate similarity of biological/biotechnology-derived products. The biosimilar approach, based on a comprehensive comparability exercise, will then have to be followed.

European Medicine Agency (EMA) does not regulate interchangeability, switching and substitution of a reference medicine by its biosimilar. These fall within the remit of EU Member States and each Member States influence processes of prescription of medicinal products, release to patients and processes of usage.

Switching and Automatic Substitution of Biological Medicinal Products

In the context of biosimilars and reference medicines, it is important for healthcare professionals to be aware of the terminology to refer to interchangeability and substitution practices in the EU. Interchangeability refers to the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect. This could mean replacing a reference product with a biosimilar (or vice versa) or replacing one biosimilar with another. Replacement can be done by:

- Switching, which is when the prescriber decides to exchange one medicine for another medicine with the same therapeutic intent.

- Substitution (automatic), which is the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at pharmacy level without consulting the prescriber.

IFPA opinion is that due to natural variability of the biological source and complexity of molecules of biological medicinal products the decisions on which biological medicinal product to use for a specific patient should always be taken by the treating physician.
This means that:

- the prescribing physician must always retain the option to designate which biological product should be dispensed to a patient and treatment decisions must be made first on the basis of clinical judgment and then on the overall value proposition offered by individual medicines; and

- the treating physician, in consultation with the patient, should make any decision to switch patient from one biological product to another. Where switching occurs, it must be accompanied by adequate clinical monitoring and the patient must be informed appropriately at all times.

This applies to both - original biological medicinal product and similar biological medicinal product.

Considerations for physicians on switching decisions regarding biosimilars

All biologics approved by EMA are safe, effective and of high quality. With the introduction of biosimilars, i.e. biological products that are highly similar but not identical to their respective reference product, physicians may be encouraged within the healthcare system to switch patients from a reference product to any of its biosimilars (or vice versa) to reduce costs.

To gain regulatory authority approval a biosimilar must be compared in terms of quality, safety and efficacy with its reference product before it qualifies for approval. However, there is no regulatory authority requirement for individually approved biosimilars to the same reference product to be compared with each other. Consequently, this type of data may not be available for any stakeholder to refer to when evaluating a switch between two biosimilars to the same reference product.

The complex nature of biological molecules, which are often used to treat patients who have multifaceted, chronic diseases, means that any decision to switch should be made on a case-by-case basis and must be patient, disease and product specific. A ‘one size fits all’ approach is not appropriate. Rather, it is important for the physician to balance the level of evidence against the level of risk or uncertainty in each particular case.

Knowledge of the patient history, e.g. number of previous switches, patient's co-medications and co-morbidities and the therapeutic options available all need to be taken into account when considering the switching.

There are two scenarios in which switching from a reference product to a biosimilar (or between any products within a similar group of related products) is **NOT** recommended:

- **When the initial treatment choice, e.g. reference product or biosimilar, loses efficacy or when there are tolerability issues**, switching to a similar product within the same group of related products is not recommended. This is because all of these products are expected to have similar clinical efficacy and safety to each other such that there is no incremental clinical benefit to the patient.

- **If the physician feels that on balance a switch is likely to compromise future treatment options for the patient, (e.g. with an alternate biological therapy), then a switch is not advisable,** although little is known about the consequences of multiple exposures to the same group of related products and the consequences on immunogenicity of future treatments with biologics.

Automatic substitution makes product post-marketing pharmacovigilance surveillance more difficult.

For identifying and tracing biological medicines in the EU, medicines have to be distinguished by the tradename and batch number and this is particularly important in cases where more than one medicine with the same INN exists on the market. This ensures that, in line with EU requirements for ADR reporting, the medicine can be correctly identified if any product-specific safety (or immunogenicity) concern arises.
Healthcare professionals play an essential role in contributing to the understanding of a medicine's safety profile during clinical use. Biological medicines are approved on the basis of an acceptable safety profile and they should be used according to the recommendations in the summary of product characteristics (SmPC) and package leaflet. If a suspected ADR is identified for a biological medicine, healthcare professionals should report it, taking care to include the tradename and batch number of the medicine. It is important that healthcare professionals report any suspected ADR of a biosimilar even if the reaction is already listed in the reference medicine's SmPC.
With biological medicinal products certain adverse reactions can take time to manifest, particularly those that are associated with an immune response. If automatic substitution would be applied to biological medicinal products, then repeated changes between different brand preparations and manufacturers could occur over time and would pose significant challenges to link the reported adverse event with particular preparation. Further, applying automatic substitution rules to biological medicinal products would confound traceability as the physician, who is most commonly the reporter of adverse events, may not know if substitution has taken place and could incorrectly identify the brand product. The obligation for a physician to indicate only international name of the active substance on the prescriptions would even more exacerbate the traceability.
This issue has also been acknowledged by the European Commission and the European Parliament in the new pharmacovigilance legislation which requires Member States to "*ensure, through the methods of collecting information and where necessary through the follow-up of suspected adverse reaction reports, that all appropriate measures are taken to identify any biological medicinal product prescribed, dispensed, or sold in their territory which is the subject of a suspected adverse reaction report, with due regard to the name of the medicinal product (in accordance with Article 1(20)) and the batch number*."i.
Accordingly, physicians should be involved in any decision to change a prescription for a biological medicinal product so that they are aware of when a new original or similar biological medicinal product is being administered to their patients. In such case physicians may take appropriate pharmacovigilance measures.
The IFPA supports this approach and encourages the standard reporting of brand name, manufacturer's name and batch number for all suspected adverse events of all biological medicinal products.

Automatic substitution of medicinal products interferes with a physician's full choice and freedom to prescribe particular medicinal product

As stated in the EMA guidelines, standard generic approach used to deal with generic medicines is not scientifically appropriate for biological medicinal products and these may be important for the physician's choice of the best treatment for a particular patient. Biological medicinal products are generally prescribed to patients with severe conditions, often with multiple co-morbidities. A physician may have reviewed the available clinical data and prescribed a specific brand for his or her patient as a consequence of this review and may have achieved a satisfactory stable clinical situation for the patient. It is therefore important that this choice is respected by the healthcare professional such as the pharmacist when the medicine is dispensed.

The IFPA considers that the physician is best placed to assess the patient, disease and product, when deciding if and how to switch the biological product that a patient is receiving for another one. Therefore, the physician should retain decision-making autonomy and have unrestricted choice of products to prescribe. The physician should balance the level of risk and related uncertainties against the availability of evidence on a case-by-case basis.
The IFPA considers that physicians' freedom to choose what they believe to be the most clinically appropriate products for their patients must be respected and maintained.

Patients have a right to be informed about prescribed medicinal product

Patients need to be adequately informed about their treatment. If the drug treatment is changed during the course of therapy or if substitution of one product for another takes place, patients must be adequately informed in order to favor compliance and adherence to treatment as well as ensuring they are aware in case of unexpected adverse reactions. In addition, patients have a right to be informed of the advantages and disadvantages of the different products that may be administered, particularly the newest information related to safety. This is particularly relevant for patients with long-term treatment, often suffering from several diseases, who have been stabilized on a given treatment and may be more resistant to a change from an accepted treatment.

Conclusions

Biosimilar medicines can create room for innovation in the patient treatment and support the sustainability of the health system. Great social evolution (aging of society, chronic illness) increases pressure on the health system's sustainability in Lithuania, but also throughout Europe. The use of biosimilar medicines could generate, along with other procedural measures, savings which would then enable further financial investment in finding innovative medicines. Such policy should be implemented in the light of the principles that should always be taken into account in the development and implementation of procedural measures such as the continuity of patient's treatment and the role of physicians as decision-makers.
An effective pharmacovigilance system (PV) of biological medicines is important, especially when several treatment options are available. Tracking of medicines is crucial for biological medicines. Yet, much of this effort lies on an efficient PV system and on safe reporting practices not only of regulatory bodies, but also of health professionals, patients and the general public.

The IFPA is open for discussions in order to establish rules fostering honest competition and patients' access to safe biological medicinal products. Also, it is necessary to ensure market environment that maintains reasonable incentives for scientific research and development of treatments and prevention for diseases impacting patients and society.

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