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Automatic substitution of biological medicines at pharmacies

Views on potential automatic substitution and the related medication safety aspects

The total sales of medicines have grown in Finland during the 2010s. In 2017, the total sales were nearly EUR 3.1 billion. Measured at wholesale prices in euros, there were eight biological medicines among the ten best-selling medicinal products in Finland. For most of them, there are copies available that are also known as biosimilars, which have been proven to be comparable with their reference medicines as far as their quality, efficacy and safety are concerned. The uptake of biosimilars will initiate price competition between biological preparations, which has significant implications on the national economy.

Why was this survey conducted?

According to the Programme of Prime Minister Juha Sipilä's Government (2015–2019), a Rational Pharmacotherapy Action Plan was implemented in Finland, one objective of which was the promotion of the uptake of biosimilars. However, the uptake of biosimilars in ambulatory care has remained sparse. Consequently, the Action Plan noted that the information-based guidance provided to date and the concurrently implemented legislative amendments were not sufficient to promote the uptake of biosimilars.

Following the entry into force of a decree in the beginning of 2017, Finnish doctors have been obligated to prescribe a more affordable comparable and alternative (similar) biological medicine if available. However, according to a recent study conducted by Fimea, it appears that doctors do not perceive the current regulations as sufficiently binding (Sarnola et al. 2019). Additionally, the fact that the difference in price between a biological reference medicine and it´s biosimilar is perceived as being too small reduces the willingness to prescribe biosimilars.

The bioequivalence that is a necessary precondition for the interchangeability of biological preparations is already demonstrated for the biosimilar and it´s reference product as part of the biosimilar development process. Consequently, the Finnish Medicines Agency Fimea has outlined that biosimilars are interchangeable and therapeutically equivalent with the help, and under the supervision, of a health care professional (medical doctor). Automatic substitution at pharmacies has not yet been applied to biological medicines in ambulatory care in Finland other than with regard to parallel-imported and parallel-distributed products.

The purpose of this survey was to map out views on the potential automatic substitution of the biological medicines used in ambulatory care, especially from the point of view of safeguarding medication safety.

Material and methods

The views of Finnish pharmaceutical operators and patient organisations on the automatic substitution of the biological medicines used in ambulatory care were studied with semi-structured interviews conducted in the autumn of 2018 (a total of 32 individual, pair or group interviews with 62 people participating in them). The views of the following operators were considered relevant to the study: pharmacies, prescribers, nurses, patients/clients/medicine users, the pharmaceutical industry, pharmaceutical wholesalers, authorities and hospital pharmacies. In the analysis, factors that need to be taken into account if the automatic substitution of biological medicinal products at pharmacies would be considered were identified from the material.

Results and discussion

The interviewees who were most critical of the possibility of automatic substitution saw a lot of risks in the substitution that could not be reasonably mitigated by any means. Some of the interviewees maintained that there is not yet enough experience available on biosimilars, so automatic

substitution would not be relevant at this point but could be possible after a few years. Some of the interviewees considered the Finnish pharmacy system suitable also for implementing the automatic substitution of biological medicinal products. Special appreciation was given to the qualified pharmaceutical personnel working at pharmacies.

The pharmaceutical savings to society were perceived as the greatest benefit resulting from the automatic substitution of biological medicines (**Table 1**). Additionally, the use of more affordable biological medicines could make it possible to provide biological treatment to a larger group of patients. In addition to the economic benefits, benefits associated with the smoothness of pharmacotherapy were also identified in the interviews.

A number of risks associated with the substitution of biological medicines were also identified in the interviews (**Table 2**). The risk of discontinuation of pharmacotherapy for different reasons was perceived as significant, and the risk of overlapping medication was also considered possible. According to the interviewees, the differences in the accompanying materials related to biological medicines could also confuse the patient. Potential problems with the traceability of the products were also raised.

Discussion of the results from the authorities' point of view: The potential automatic substitution of biological medicines will not bring any immediate economic benefit to a patient who is already receiving biological medicinal treatment. In Finland, biological medicinal products are, as a rule, eligible for special reimbursement and/or very expensive, for which reason the purchases of biological medicinal products are largely reimbursed to the patients out of the health insurance. However, there is obvious potential for savings in the pharmaceutical expenditure of society which, in turn, enables the uptake of novel, usually expensive, medicines.

Table 1. Benefits raised in the interviews that could relate to automatic substitution of biological medicines.

Benefit arising from substitution and its description	
Pharmaceutical savings	
	Society saves in medicine costs.
Treatment becomes possible for a larger number of people	
	Lower prices may improve the patients' willingness and ability to use self-injected biological products.
	New patients can be provided with access to medicinal treatment.
	Patients may start biological treatment earlier.
	New pharmacotherapies can be taken up with the savings obtained.
Smoothness of pharmacotherapy	
	Patients may receive a three-month dose of medicines at the same time if the price of the product falls sufficiently.
	The treatment can be smoothly continued with another product if the reimbursibility of the product used by the patient changes.
	The treatment can be smoothly continued with another product if the product used by the patient is not available.
	Substitution could improve immediate availability if the pharmacies were aware of which product is to be supplied.
	The falling of prices may increase the pharmacy's willingness to keep the products in stock.

Table 2. Medication safety risks identified in the interviews that may be related to the automatic substitution of biological medicinal products, and potential means for mitigating the risks raised in the interviews.

Risk description	Example	Risk mitigation
The patient's pharmacotherapy is discontinued momentarily or permanently		
The patient does not trust the new medicinal product	• The substitution comes as a surprise at a pharmacy. • The patient receives conflicting information about the substitution from different health care professionals. • The patient has obtained considerable benefit from the reference product and does not want to substitute it.	• Consistent, positive attitude towards substitution in health care and at different pharmacies • A proactive discussion on the substitution with the patient by a physician and a nurse • Supplementary training on biosimilars for health care professionals
The patient experiences adverse reactions as a result of substitution	• Reactions to an excipient used in the preparation • Nocebo effect • Large-scale substitution may reveal problems that were not previously detected	• Consistent, positive attitude towards substitution in health care and at different pharmacies • The patient knows where to contact in case of problems • Substitution is avoided at the commencement of medicinal treatment • The success of the medicinal treatment is monitored • Post-marketing control of medicinal products
Concern about losing the efficacy of the medicine	• The formation of pharmaceutical antibodies is accelerated as a result of the substitution	• The patients are monitored • A substitution interval is defined for biological medicinal products that would be longer than in generic substitution
The patient is unable or incapable of using the dosing device correctly	• The patient experiences the new device as difficult to use • The device is unsuitable for the patient (handicap, visual impairment) • The dose is wasted	• Pharmaceutical advice, injection instruction • A substitution interval is defined for biological medicinal products that would be longer than in generic substitution • Assessment of the interchangeability of devices in a regulatory process • Ban on substitution imposed by a physician when necessary • Checking of the ability to use the device at every pharmacy visit
The medicinal product is not available	• The pharmacy does not have the product in stock • The product is not available in Finland	• Dispensing of biological medicinal products at the pharmacy by a separate appointment • Mandatory reserve supplies of biological medicines • Implementation of substitution in such a way as to allow pharmaceutical companies to anticipate the markets (cf. the length of the chosen substitution interval)
The patient uses two medicines concurrently		
Similar/different packaging and names	• Difficult names of the active substance • Trade names that differ from one another • Established trade name	• Substitution is marked on the new packaging with a substitution sticker • Pharmaceutical advice at the pharmacy • Use of model devices when providing pharmaceutical advice (visuality)
The patient does not understand that a substitution has been made	• Patients with polypharmacy, the elderly, patients with cognitive impairment	• Ban on substitution imposed by a physician when necessary • It is ensured in connection with the pharmacy's pharmaceutical advice that the patient/medicine administrator understands the substitution • The new product is not dispensed too early so that the patient will not have two overlapping medicines concurrently available at home
The patient has two prescriptions for the same active substance	• The patient has a prescription for the reference product and another one for a biosimilar	• Cancellation of the old prescription at the pharmacy upon dispensing

Table 2 continues

Risk description	Example	Risk mitigation
The patient becomes confused with the supporting material received		
There may be differences in the written material received by the patient	• The patient receives a wealth of material concerning different products	• Generic, harmonised risk minimisation material
The availability of supplementary materials may vary product-by-product	• The pharmaceutical company provides supplementary material, such as internet pages, storage and transport boxes	• No risk mitigation means were proposed in the interviews
The product used cannot be traced if problems occur		
If the patient gets adverse reactions, the product cannot be traced	• The physician is not aware which product and batch the patient has used • Established trade name	• Checking of the trade name of the supplied medicinal product from the Prescription Centre • Development of information systems in such a way that the batch number of the supplied product will also be registered in the digital Kanta prescription service* • Deployment of the Medicines Verification System (automation of the recording of the supplied batch)
Delayed onset of adverse reactions to a biological medicinal product	• The preparation causing the adverse reaction cannot be determined	• A substitution interval is defined for biological medicinal products that would be longer than in generic substitution • The substitution is carried out for patients whose treatment is in balance
The patient is not provided with any substitution-related counselling from the pharmacy		
Those acting on behalf of the patient	• The medicine can be collected on the patient's behalf by a family member, for example	• Written material • Ban on substitution imposed by a physician
New ways of dispensing the medicine	• The patient may collect the medicine from a 'smart box' at their convenience	• No risk mitigation means were proposed in the interviews
The patient has no access to health care if problems occur		
Substitution increases the number of patient contacts with health care	• Substitution may give rise to concerns for the patient and a need to discuss the substitution in health care • The patient contacts a doctor in order to have a ban on substitution imposed	• The patient's trust in the new product is confirmed • Pharmaceutical advice
*Please refer to www.kanta.fi		

Discussion of the results from the authorities' point of view: Many of the comments made in the interviews suggest that objective information on the comparability of biological reference medicines and their biosimilars has not reached all the pharmaceutical operators well enough. This is evidenced, for example, by the comments on the as yet unknown safety concerns related to large-scale substitution, and on the acceleration of the development of pharmaceutical antibodies.

There is currently more than ten years of experience in the use of biosimilars. There is also a wealth of experience and published information on one-off switches between a reference medicine and its biosimilar. In these studies, the substitution of the reference medicine by a biosimilar has not increased immunogenicity. However, the information available on recurring substitutions remains sparse to date, but the available research data does not give cause for concern. Additionally, antibody assays can be used after substitution to monitor therapy in the same way as before the substitution.

The pharmacological time profile of the potential adverse effects of biological medicinal products and the burden

caused by the substitution to the patient and pharmacies should be taken into account when the potential implementation of automatic substitution is assessed. This can be influenced by defining a longer substitution interval for biological medicines than for generic products. In this case, for example, linking potential adverse effects with the product that potentially caused them would be easier in practice.

The starting point is that switching from a reference medicine to its biosimilar or vice versa will only be carried out when the patient has achieved a satisfactory therapeutic response with the original pharmacotherapy. This is to avoid interpreting the symptoms that patients easily experience at the commencement of any pharmacotherapy as resulting from substitution. As it is, the biosimilar will be just as good and just as bad as the corresponding reference medicine.

Medicines information

Based on the research data available on generic substitution, informing patients and ensuring the consistency of the medicines information received from different sources is of crucial importance when the automatic substitution of biological preparations is considered.

Biological medicines often have statutory risk minimisation material intended for the patient and/or health care professionals to promote the safe use of the medicine. The new regulatory guidelines require that the risk minimisation materials for biosimilars are as similar as possible to those of the reference product. Furthermore, the material must be as generic as possible, and no commercial elements are allowed in the material. However, there are also materials approved under the old guidelines still in use that may differ from one another and make a strong reference to the trade name of the product. However, when the materials are updated, the materials of reference products and biosimilars will be harmonised with regard to their appearance as well, which should reduce patient confusion in substitution situations in particular. Thus, an EU-wide will to harmonise the risk minimisation materials is a factor contributing to medication safety from the perspective of potential automatic substitution.

Administration devices

The usability of administration devices is tested as part of the product development aiming at marketing authorisation, and the suitability of the administration device is assessed by the authorities at the marketing authorisation stage. However, for the time being, functional similarity between the administration device of a reference medicine and that of its biosimilar is not assessed as part of the biosimilar marketing authorisation process, due to which clinically significant and/or user-experience related differences in their operation are possible.

Clinically significant dose variations are possible in substitution if the patient is not provided with sufficient guidance on the use of the new administration device. However, most biological medicines have a gradual dose response, so the clinical significance of temporary, small dose variations remains minor. In insulin therapy, the therapeutic range is narrow, so even small dose variations are clinically significant. However, in insulin therapy, the patient's therapeutic response is continuously monitored by blood glucose measurements. Any significant differences in medication safety between the dosing device of the reference medicine and that of the biosimilar should nevertheless be taken into account when the interchangeability of the product is assessed.

According to the Medicines Act currently in force in Finland (395/1987, section 57b), the prescriber of the medicinal product may forbid substitution on medical or therapeutic grounds by making an entry to that effect in the prescription. Similar consideration would also be possible for the prescriber in the event of a substitution of biological products in cases where, for example, the patient has been diagnosed with a sensitivity to excipients. In the substitution of biological medicinal products, the prescriber's consideration also includes an assessment of the patient's ability to replace the administration device safely.

In the case of substitution, the patient should, if necessary, be provided with instruction on the use of the administration device at the pharmacy. However, if the medicine is collected on the patient's behalf by someone else or dispensed in a new way, the pharmaceutical personnel at the pharmacy will have limited opportunities to check whether the patent is able to use the administration device correctly. This challenge pertains to current pharmaceutical advice as well, but its significance may be pronounced in the potential automatic substitution of biological medicinal products.

Traceability

In connection with the supply of biological medicines, the pharmacy is already required to ensure that the batch number of a biological medicine supplied to the customer can be determined for a period of five years after the supply of the medicine. In February 2019, a package-specific unique identifier was also introduced in the EU, which improves the traceability of medicines intended for human use.

In general, the traceability of biosimilars and their reference medicines is good at the product level, and biosimilar batches are not any more difficult to trace than batches of the reference medicine. Where necessary, the doctor may check the trade name of the product supplied from the pharmacy from the national e-prescription centre.

Other concerns

Other challenges were also raised in the interviews that relate to the current generic substitution practice and would therefore not be specific to the substitution of biological medicines. Examples include concerns about the concurrent use of overlapping medicines and the shortage of resources in health care in situations where problems related to substitution arise.

According to the interviewees, the factors affecting the suitability of a biological medicinal product for automatic substitution include the characteristics of the active substance, the composition, quality, intended use and route of administration of the medicinal product, and the special characteristics of the administration device (**Table 3**).

Short substitution interval was considered to impair medication safety. In particular, the mastering of a new administration device, problems with product- and batch-specific monitoring and traceability, the wealth of product-specific materials received by the patient, and the characteristics related to the pharmacology of the product were perceived as risks posed by a short substitution interval. On the other hand, the interviewees also pointed out that if the substitution interval is too long, the whole idea of automatic substitution may suffer, as there will not be enough competition between products.

The interviewees raised the possibility of starting the patient's medicinal

Table 3. Views expressed in the interviews on the characteristics of a biological medicinal product that should be taken into account when the suitability of the product for automatic substitution is assessed, completed with the regulatory authority's remarks.

Description of the characteristic	Regulatory authority's remarks on the characteristics raised in the interviews
When the size and complexity of the molecule increases, the medicine will be less suitable for substitution	The similarity of the characteristics of the biosimilar and the reference medicine is already ensured in the marketing authorisation process.
The narrow therapeutic range of the medicinal substance may result in severe consequences in the event of dosing errors	Those biological medicines with a marketing authorisation for which biosimilars are/will be available usually have a wide therapeutic range (e.g. infliximab) or their therapeutic response can be monitored by the patient (e.g. insulins). However, the possibility of a clinically significant dosing error should always be assessed when deciding on product specific substitution.
Potential substitution-related immunogenicity	The similarity of the immunogenicity of a biological medicinal product and its biosimilar is already ensured in the marketing authorisation process. So far, no increase in immunological adverse effects has been observed in connection with switches between products.
Excipients included in the product	The suitability of excipients for clinical use is evaluated in the medicinal product´s marketing authorisation process. However, in practice, there may be differences between the excipients used in interchangeable products the same way as between the products currently included within the range of generic substitution. If the patient is aware of any sensitivity related to the excipients used in the product, the attending physician should prohibit substitution on medical grounds.
Proteins included in the product	It is ensured as part of the marketing authorisation process that the active substance (protein) contained in the biosimilar is highly similar to the active substance of the reference medicine.
Quality of biosimilars in general	Evaluated as part of the marketing authorisation process. The same quality criteria apply to all biological medicines, including reference medicines and their biosimilars.
Variation between batches	There may be a certain degree of intrinsic variation between different manufacturing batches of all biological medicines owing to the complexity of their structure and the production method.
Products that are frequently dosed are better suited for substitution, because the user of the medicine will easier develop a routine for it.	There is currently no research data available on the role of the development of a routine as opposed to safe implementation of the automatic substitution of biological medicines. Furthermore, biological reference medicines and their biosimilars are administered in the same way. Therefore, when suitability for substitution is assessed, rather than the method of administration, the key issue will be the suitability of the administration devices for substitution.
Differences in indications and extrapolation of the indication	As a rule, a biosimilar authorised in the EU is granted the same indications as approved for its reference medicine and only insofar as its efficacy and safety can, with sufficient certainty, be expected to be comparable in the extrapolated indications as well.
Ease of use	Any differences in the usability of the dosing devices of the products should be taken into account when suitability for substitution is assessed.
Similarity with other interchangeable devices	Any differences in the safety of use of the dosing devices of the products should be taken into account when suitability for substitution is assessed.
Suitability to different patient groups	Any differences in the suitability of the dosing devices of the products to different patient groups should be taken into account when suitability for substitution is assessed.

Table 3 continues

Description of the characteristic	Regulatory authority's remarks on the characteristics raised in the interviews
Ancillaries accompanying the device	A product with a marketing authorisation is usable as such and does not require other ancillaries. The ancillary products and services offered by the pharmaceutical industry are not relevant insofar as substitution is concerned.
Possibility for self-monitoring and adjusting the dose where necessary	The characteristic is relevant in situations where the replacement of the administration device could involve clinically significant dose variation and should therefore be taken into account when suitability for substitution is assessed.
Development of other products in the therapeutic range and the possibility of switching to another medicinal substance where necessary	In the opinion of the authorities, the characteristic is not relevant insofar as substitution is concerned.
Nationally implemented risk minimisation material related to the marketing authorisation	According to the current regulatory guidelines, the risk minimisation material for a biosimilar should be generic and as similar as possible to that of its biological reference product. However, materials approved under the old guidelines are still in use, and their appearances may vary between biological medicinal products that are otherwise mutually comparable. However, when the materials are updated, these appearances will be harmonised as well.

treatment with a biosimilar, either in such a way that a physician prescribes the medicinal product based on the active substance of the biological medicinal product (generic prescription) or that the product prescribed by a physician is substituted at the pharmacy by a more affordable similar product when the first prescription is dispensed. However, some of the interviewees noted that the uptake of biosimilars in new treatments only is not a very effective way to promote the use of biosimilars.

The interviewees noted that following the potential substitution of biological medicines, the duties and responsibilities of health care professionals involved in medicinal treatment, especially in device advice, would change from the present.

> *The starting point is that switching from a reference medicine to its biosimilar or vice versa will only be carried out when the patient has achieved a satisfactory therapeutic response with the original pharmacotherapy.*

Discussion of the results from the authorities' point of view: Under the current Medicines Act (395/1987), Finnish pharmacies are required to ensure, through advice and guidance, the correct and safe use of the medicine. This applies to all medicinal products supplied, including all biological medicinal products. However, based on the interviews, it appeared that there is still uncertainty as to the responsibilities concerning injection instruction and ensuring the correct and safe use of the administration device of the biological medicine, and cooperation between pharmacies and health care organisations has not necessarily been agreed upon. From the point of view of safeguarding medication safety, it would be most practical that, even in the case of potential automatic substitution, the patient would have the opportunity to receive guidance already in the health care unit in the use of the administration device for the product the patient will actually use.

Deciding the length of the substitution interval for biological medicinal products and how it is to be instructed is critical if a decision is made to implement the automatic substitution of biological medicinal products at pharmacies. Although there is currently no scientific evidence or clear theoretical basis for immunogenicity provoked by a short substitution interval, neither is there any extensive experience on recurring automatic substitution with a short substitution interval implemented in long-term treatment.

When the substitution interval is determined, not only medical, but also administrative and practical aspects need to be considered. From a medical point of view, the proper time to carry out the substitution is when the patient's therapeutic response with the currently used medicinal product is in balance and satisfactory. On the other hand, when a new medicinal treatment is started, the substitution can be carried out automatically at the pharmacy when the first medicine package is collected with no medical impediments involved with the treatment phase.

Recommendations

Based on this survey, Fimea holds that it is possible to implement the automatic substitution of biological medicines at pharmacies gradually while safeguarding medication safety subject to the following conditions:

1. Fimea determines the clinical and practical interchangeability of biological medicines. This also includes an assessment of the functional similarity of the administration devices.

2. The substitution is carried out at pharmacies. The pharmacies ensure that the existing legal obligation to provide the customer with pharmaceutical advice is duly fulfilled when any biological medicinal product is dispensed. This also includes guidance on the correct and safe use of the administration device of the medicinal product concerned. Where necessary, the expertise of pharmacy personnel must be supported by means of new tools and systems that guide the safe implementation of the substitution.

3. The substitution is always carried out at the pharmacy upon commencement of a new biological medicinal treatment when the first prescription is dispensed. For an existing medicinal treatment, the medically justifiable substitution interval could be one year, for example. However, the prescriber may exercise discretion and forbid automatic substitution for medical or therapeutic reasons the same way as in the current generic substitution.

4. The correct and safe use of the administration device is also ensured at pharmacies if the medicine is collected on the patient's behalf by someone else or dispensed in a new way.

5. It is ensured between pharmacies and other health care units that the patient is provided with both consistent medicines information and guidance in the use of the administration device for the product the patient will actually use.

6. The flow of information between the parties involved in medicinal treatment (doctor, nurse, pharmacy personnel) is more effective and structured than at present.

7. Biosimilar competence of all those who are involved in medicinal treatment (doctor, nurse, pharmacy personnel) is developed by ensuring the availability of, and access to, objective biosimilar information by means of both basic and supplementary education and training. Administration device competence is also to be ensured.

Based on the survey, the uptake of automatic substitution of biological medicines is possible, but careful planning and possibly gradual implementation would be required. The objective should be to safeguard medication safety by means of a system that will not unnecessarily burden the parties involved in the substitution, but allows for cost-effective medicinal treatment from an individual and societal point of view without compromising the effectiveness of the patient's medicinal treatment.

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FURTHER READING

- Sarnola K et al. [Uptake of biosimilars in Finland – Physicians' views.] Finnish Medicines Agency Fimea. Serial Publication Fimea Develops, Assesses and Informs 4/2019. 44 p. ISBN 978-952-7299-02-9.

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