What Has Changed with the Current Regulation on Licensing and What Should Companies Consider When Determining Their Strategies?

ÇETİNKAYA

ASN

The Regulation on the Licensing of Medicinal Products for Human Use

On 11 December 2021, the "Regulation on the Licensing of Medicinal Products for Human Use" ("**Regulation**") was published in the Official Gazette No. 31686 by the Turkish Medicines and Medical Devices Agency ("**TİTCK**" or "The **Agency**").

The Regulation, which aims to determine the procedures and principles applied in regulatory affairs and the practices regarding authorized medicinal products for human use ("**medicinal products**"), has been prepared in line with harmonization studies with European Union legislation, taking into account Directive 2001/83/EC of the European Parliament and of the Council dated 6 November 2001 on Medicinal Product for Human Use and the Commission Regulation 507/2006/EC of 29 March 2006 on the Conditional Marketing Authorization for Medicinal Products for Human Use.

The Regulation is important in terms of consolidating the additions made to the previous regulation published in 2005 and the practices developed in TİTCK announcements in a uniform language. In short it contains important provisions related to definition changes/additions, shortened application types, innovations in application evaluation procedures and principles, processes and requirements for license renewal and suspension, conditional licensing, exceptional license procedure and jointly marketed products, which will be important for companies developing their current and future strategies.

Which Regulations Will Be Implemented When?

In line with Article 45 of the Regulation titled "Enforcement", the provisions of the Regulation entered into force on 11 December 2021, the date of publication.

However, according to Article 22, which regulates the suspension of licenses:

- provision 1-i which regulates situations in which at least one commercial batch of a product has not been placed on the market within 30 months of the date of its registration and
- provision 1-j which regulates cases that determine a licensed product under the QR code application is not on the relevant market or fail to submit official documents indicating that the licensed product has been released to the market for products outside the scope of the QR code application to the Agency

will enter into force on **11 December 2022**.

However, in accordance with paragraph 1 of Article 29, which regulates the

marketing authorization for blood products, the requirement for a license/permit holder to apply to the Agency to obtain a marketing authorization for each batch of the product, in addition to obtaining a sales permit before placing the product on the market will come into force as of **1 January 2025**.

What Prominent Arrangements in the Regulation Will Affect Companies?

The regulation evaluates important changes and new applications that may affect the portfolio strategies of companies' management under five headings.

1. Co-marketing

An increasing practice among national and international companies, co-marketing has been included in the new Regulation in more detail. The main reason for the introduction of new regulations in this regard is the increasing importance of co-marketing in companies' growth and portfolio expansion strategies. This increase has created the need for standardization and greater MoH control.

These changes substantially reinforce the principle that a product that is co-marketed is a complete reflection of the existing main product. While co-marketing remains a crucial option in the pharmaceutical market, where generic/equivalent product competition is increasing, companies should review their existing and planned collaborations in respect of these new rules and reevaluate co-marketing's place in their growth strategies.

When examining the current Regulation, arrangements regarding co-marketing include:

- Precautions and commitments to move co-marketed products away from the main dossier; with these regulations, the aim is to prevent a co-marketed product from acting as an independent product by moving it away from the main file on content, process, place of manufacturing and similar issues.
- Co-marketing applications are limited to authorized products only. With this change, it can be said that co-marketing agreements made to simultaneously launch products while they are still in the R&D and license stage, of which there are many examples in the sector, have been blocked. Thus, the advantage of an early launch by means of co-marketing is eliminated, provided that companies can only receive common marketing files of existing products.

- While a co-marketing application could be made with Module 1 in the previous regulation, a full and complete file application option has been included in the new regulation. The advantage of full and complete file and co-marketing applications is that even if the main file is withdrawn from the market, marketing activities for the co-marketed product can continue.
    - Under Provisional Article 5, a certain period of time is given to companies that wish to benefit from this advantage on a one-time basis in order to convert their applications into full and complete dossiers. A 30-day period is given for products with applications made under Module 1 that are still in progress, and six-month period is given for products that are already licensed.

2. Regulations for Combinations

In the past 20 years, companies have used combination products effectively as a portfolio expansion method, and these products have reached a significant point in drug use.

Regulatory authorities also try to control these combination products, which have significant turnover figures with both the Social Security Institution and the TİTCK discussing their requirements and scientific regulations from time to time. As a continuation of this approach, a number of new rules regarding combination products were introduced in the Regulation.

- It has become mandatory to submit applications for fixed combination products with appropriate bioavailability or bioequivalence data, as well as literature information indicating that such active substances are effective and safe when used together, and any retrospective studies with data collected from hospitals in Turkey. If the TİTCK finds the studies submitted to be insufficient, it is obligatory to present the results of clinical studies conducted with the new combination, the scope of which is determined by the TİTCK.
- The results of clinical studies, and where necessary, preclinical tests, must be submitted in fixed combination applications for medicinal products containing active substances that have not previously been used together for therapeutic purposes.

With these regulations, while the place of combination products in treatment is accepted, companies are directed to the necessary evaluations and studies regarding their scientific necessity.

3. Regulations on Emergency Use (Exceptional and Conditional Licensing)

Practices that we have experienced more closely with the COVID-19 pandemic, especially when it comes to public health, have shown the importance of urgent access to vital drugs for patients, their relatives, health providers, and health authorities.

The procedures to follow, which were brought into practice with a temporary article in the previous regulation are clearly defined in the current Regulation with a guide provided to companies regarding emergency, and exceptional access to medicine. The procedures and principles regarding this issue are outlined in the section 24 of this article.

4. Suspension and Cancellation of Licenses

The Ministry of Health ("**MoH**") aims to eliminate products that are no longer important, that are not active, that have not been updated, and that are a burden to companies and the MoH, for purposes similar to the "Sunset Clause" in European practice.

In this context, licenses for products that are not on the market for a period of 30 months may be suspended and then may be revoked if the relevant company does not fulfill its commitment.

Articles 15 and 16 of this overview describe this in more detail. According to this new condition, companies should regularly review plans to remove their products, and unused files from promotion or sale. Additionally, the transfer and similar cooperation options for idle products and licenses should be evaluated in a timely and strategic manner.

5. License Transition Applications for Products in Intermediate Status

Since the Regulation for Traditional Herbal Medicinal Products came into force in 2010, it has been stated that the process of the transition applications for the products with intermediate product status to medicinal product for human use licenses will be extended for one more year in accordance with Provisional Article 1 from the date of entry into force of the Regulation, afterwards permits or license applications will be revoked. The provision aims to prevent intermediate products that do not currently meet the requirements for transitioning to the status of the medicinal product, from being on the market.

6. Environmental Risks

For the first time, the Regulation includes "environmental risks" under the risks related to the use of medicinal products in the definitions article.

In fact, environmental risks and compliance with them were included in previous regulations and presented as an issue with which compliance was mandatory within the framework of the relevant sub-legislation. However, this regulation, which is a reflection of compliance with the current Regulation and the European Union legislation is a strong signal that the environmental procedures and certification processes that companies must comply with at all stages of production, storage, consumption and post-consumption may increase in future and may be included in the relevant regulations as a prerequisite.

In this respect, it is important for companies to review their processes and functions related to environmental risks in the way they do business and to be prepared for possible additional obligations.

What Does the Current Licensing Regulation Introduce?

7. Exclusions and Scope Evaluation Criteria

The additions made to the scope article clearly state that the Regulation does not cover:

- Traditional herbal medicinal products,
- Homeopathic medicinal products,
- Foods for special medical purposes, and
- Advanced therapy medicinal products.

It is expected that new regulations and/or guides will be put into practice for these product groups in the upcoming period. As a matter of fact, the TİTCK published the Homeopathic Medicinal Products Licensing Regulation in the Official Gazette No. 31699 on 24 December 2021, and it entered into force.

Furthermore, given all the characteristics of the Regulation in order to evaluate its applicability, it is stated that the provisions of this Regulation shall apply where there is doubt that a product falls into the definition of medicinal products or a product definition within the scope of other relevant legislation.

Another issue that stands out as an important change is the "skin tests related to the application of allergens to the skin for the diagnosis of allergy with personal allergen products" is included in the Regulation, which was excluded from the scope with the

amendment dated 8 January 2020.

8. Definitions Newly Added and Revised

The current Regulation has included some new terms and rewritten the definitions of some of the terms already included.

The highlights in this respect are:

- The term **Reference Medicinal Product** replaces Original Medicinal Product; and the term **Equivalent Medicinal Product** replaces Generic Medicinal Product.

- **Risks associated with the use of a medicinal product,** are defined as risks to the health of patients or to public health relating to the quality, safety and efficacy of the medicinal product, or risks that may cause undesirable effects on the environment.

- While the **place of manufacture** was previously stated as the place of batch release, in the Regulation it is expressed as "*The place where the pharmaceutical form (bulk product) of the medicinal product is manufactured before the inner packaging, except in cases where the medicinal products manufactured with technologies that are not available in Turkey or are scarce, are evaluated on the basis of application by the Institution*". In this case, the definition of the place of manufacture for the products manufactured with technologies that are not available in Turkey, will be decided by the TİTCK.

- Another prominent change is in the definition of **co-marketed product**. The amendment abolishes the application of the common marketing procedure for products at the license stage, and states that a co-marketing agreement can only be made with an authorized product.

- In addition, **the international nonproprietary name ("INN")** is defined as the international name of an active substance that is accepted or recommended by the World Health Organization ("**WHO**"), that cannot be proprietary and should not be used in trademark registration in accordance with WHO rules. The **common name** term is defined as the name of the active substance in classical sources accepted as scientific reference, when the INN or INN recommended by WHO is not available.

- Lastly, other prominent additions are the definitions of "*Pharmacopeia*", "*Herbal drug*", "*Herbal preparation*", "*Herbal medicinal product*", "*Allergy Products*", "*Biosimilar products*", "*Hybrid application*" and "*Priority evaluation board*".

9. License Obligations and Applications

Regarding license obligations, the new Regulation does not include the license holder's obligation to notify the MoH that a product is on the market, or the MoH's requirement to notify the license holder that this information has been recorded within five working days.

In addition, it has been stated that if a registration application is made for the industrial manufacturing of products by persons other than the current permit holders for magistral radiopharmaceuticals, the permits granted before the issuance date of the license will continue to be valid, provided that they comply with the relevant guidelines.

However, if there is a supply problem in the market despite the authorized radiopharmaceutical product being put on the market, permission may be requested for up to 12 months, provided that its use is limited in the relevant health institution without seeking a license for the products approved by the Agency. In this context, the permissions granted by the Agency shall be valid within the period during which the existing personnel qualifications and infrastructure declared as of the date of application are maintained.

The Regulation includes electronic applications and application fees, which are currently in practice. Subject to a fee, the Agency may give "scientific advice" to an applicant before a registration application or during the registration process. This will save time and prevent financial losses, contributing to the smoother and safer execution of processes for both the Agency and the license holder.

Another new practice requires compliance with the Agency to determine that a medicinal product that does not have an authorized equivalent is not subject to a prescription before applying for a registration.

Registration applications will only be accepted electronically, except in cases deemed necessary by the Agency, force majeure or obligatory conditions, and all correspondence during the registration process will be carried out solely in the electronic environment.

Finally, the updates and additions made to the definitions and requirements, have brought the abbreviated application body into line with European Union legislation. The mentioned application types are as follows:

- Application with informed consent,

- Established medical use application,
- Allergen product application,
- Equivalent medicinal product application,
- Hybrid application,
- Application for biosimilar medicinal product, and
- Fixed combination application.

10. Prominent Changes to the Information and Documents Submitted in an Application

The information and documents required for an application by real or legal persons to obtain a registration for a medicinal product are detailed in the new Regulation, as in the previous regulation. The prominent requirements are as follows:

- A Registered Electronic Mail ("**REM**") address has been added instead of an e-mail address for license applications made to the TİTCK.
- In cases where the applicant is a legal person, the obligation to present the establishment purposes of the company has been removed.
- Manufacturing site names are requested for all manufacturing steps.
- The definition of the control methods made by the manufacturer should be presented in accordance with the pharmacopoeia.
- It has been added that preclinical test results must be submitted in addition to clinical studies, and an applicant declaration is required stating that ethical requirements are met within the scope of legislation in cases where clinical studies are carried out abroad.
- Changes have been made in the documents relating to the importation of a product, and its manufacture under license.
- In applications for co-marketed medicinal products, a commitment obligation has been introduced requiring that medicinal products subject to co-marketing are identical, all variation applications should be made simultaneously, and if the product subject to co-marketing has more than one site of manufacture, the manufacturing must be carried out in only one of these places.
- For applicants who do not have a Nuclear Regulatory Authority registration for

radiopharmaceutical products, if it is necessary to authorize a company licensed by the Nuclear Regulatory Authority:

- For the distribution and sale of radiopharmaceutical products which are manufactured, and
- For the importation, distribution and sale of the imported radiopharmaceutical products,

the contract between the two companies, in which the Nuclear Regulatory Authority-licensed company is the sole authority for the said transactions, and the registration certificate of the parties has been added to the required documents.

- Statements and other documents that are required to be submitted within the scope of the legislation regarding the active substance manufacturing sites are shown,

- The status of imported or licensed products for which an application is made, before the authorities of other countries and the information and documents sought in this regard have been counted,

- It has been regulated that within the scope of the relevant legislation, documents relating to pharmacovigilance and information pertaining to the science service in this respect, documents relating to exceptional licensing and conditional licensing where applicable, and assessment of potential environmental risks should be submitted.

- The principle of submitting all documents in Turkish is stated and documents submitted from abroad must be apostille annotated or approved by the consulate.

- The elements that should contain the summary of product characteristics ("**SPC**") are listed in a more detailed way by comparison to the previous regulation.

11. Evaluation of Applications and Licensing

Although the provisions in the Regulation for the evaluation and registration of applications were present in practice through previous announcements, attention should be drawn to some important changes.

Regarding **the preliminary evaluation of an application,** it has been stated that applications can be made throughout the year, but the license process can only be initiated by the TİTCK in February, May, August, and November, taking capacity into

account.

In addition, it has been stated that whether an application file is a complete application in terms of the documents that must be submitted according to the nature of the application and the electronic registration application requirements will be evaluated by the TİTCK in order of the application date.
However, the Priority Evaluation Board has stated that preliminary evaluation procedures will give priority to applications deemed appropriate as priority or high priority in registration procedures.

No changes were made to the 30-day period determined for the evaluation of an application file, the completion of a missing application and the second preliminary evaluation after the rectification of deficiencies.

The reasons for **rejecting an application due to the procedure** have been expanded and the following are listed:

- failure to rectify deficiencies after the first preliminary evaluation, or to rectify the deficiencies but not to make a second application within 30 days,

- failure to pay the license fee within 60 days of official notification of the completion of the license process,

- Failure to submit information and documents requested outside of the preliminary evaluation process, or an explanation regarding the failure to submit the information and documents, together with the date of submission, to the TİTCK within 30 days.

Thus, while the 30-day time limit previously only applied to the preliminary evaluation process, the new Regulation has imposed time restrictions on all correspondence made in applications for which the license process has started.

These arrangements will allow the registration processes to be concluded in a shorter time and to achieve more systematic progress. It is important in terms of preventing the prolongation of licensing products that cannot be registered due to the time-limit requirements and the reasons stated in the relevant parts of the Regulation.

The registration period remains as 210 days from the date of the letter from the TİTCK stating that the process has started for complete applications that have been accepted after the evaluation has been completed. It should be noted that the time taken for analysis within the company, as well as the time taken for evaluations by

external organizations other than TİTCK, the time taken for public holidays excluding weekends, and the time for extraordinary situations will not be included in the licensing period.

For co-marketed products, the said period is 90 days from the letter received from the TİTCK stating that the licensing process has started.
However, these processes may change according to the Priority Evaluation Commission's decisions.

Prioritization in licensing processes, authorization procedures for products approved by the Agency's Priority Evaluation Board will be completed within the timeframes specified in the prioritization guide. In addition, in cases where additional information and documents are requested from an applicant, the licensing period will be suspended until the said information and documents are obtained.

12. Dismissal of an Application on the Merits

The amendments have introduced regulations regarding the dismissal of a registration application on the merits, primarily for the analysis of the medicinal product. In this context, if a medicinal product for which there is a registration application is found to be non-compliant in the first analysis, the analysis should be repeated with an improved sample taken from the company. It is stated that if nonconformity is found in the second analysis, an evaluation meeting will be held with the company's representatives about analysis methods and an analysis method for a new sample will be determined. In the event of nonconformity in the third analysis, a final evaluation meeting will be held with the company's representatives and the analysis will be made for the final time with the new method determined.

Following the completion of the analysis steps, if it is determined that the qualitative and quantitative formula inconsistencies and the declared specifications are outside of acceptable limits, the registration application will be rejected on the merits.

However, an applicant is entitled to a maximum of three written and two verbal answers for the following situations regarding the evaluation process of medicinal products. As a result of the evaluation of the documents and information submitted after an applicant's right to reply, if:

- Under normal conditions of use, the potential risk outweighs the beneficial effect of the treatment or

- Its therapeutic effect is insufficient or has not been adequately demonstrated, or
- Where applicable, its bioavailability is insufficient or
- In cases where it is determined that the similarity with the reference biological product cannot be proven in the applications for biosimilar medicinal products,

the registration application is rejected on the merits.

13. Notice of the Dismissal of the Application on the Merits and Objections

In cases where a registration application is rejected on the merits the decision is notified to the applicant with a justification. The latest amendment makes an addition to the article, making it possible to announce the reasoned decision on the Agency's website in cases where they cannot notify an applicant directly. However, the applicant has the right to appeal to the Agency against the decision within 45 days of the date of notification or announcement. If the applicant makes no objection, the application documents are returned to the owner. It is stated that if the applicant does not receive the documents, the provisions of the Regulation on State Archive Services will be applied.

In cases where an objection is made within 45 days, it is evaluated by the Agency within 90 days, and the applicant is notified of the result. During the evaluation of an objection, if deemed necessary, the applicant may be given the right of oral explanation and defense. At this point, it should be noted that the decision made as a result of the evaluation of the objection is final and no further objection can be made to the Agency regarding the said decision.

In addition, it should be noted that the dismissal of an application on the merits will not prevent the applicant from re-applying for a registration.

14. Granting the License

As a result of the examinations and evaluations, licenses are issued for medicinal products that comply with the issues stipulated in the Regulation and applicants are informed. However, Article 20 of the Regulation has introduced some exceptions regarding the issuance of licenses. Namely:

- A second license shall not be granted to the same natural or legal person, even with a different trade name, for a medicinal product authorized by the TİTCK and a

product with the same qualitative and quantitative composition in unit dose, in the same indication and in the same pharmaceutical form. Pastilles, oral sprays, chewable tablets, fish oil preparations, nicotine gums and pediatric vitamin syrups are the exception to this regulation, where there is only aroma difference and only single dose – multidose usage difference.

- However, the TİTCK will separately evaluate applications for medicinal products that are scientifically and technologically proven to be superior to an authorized medicinal product.

In this context, in the evaluating that the active substance(s) are the same, Article 4 of the Regulation, which defines the equivalent medicinal product, is taken as basis.

- It is not possible for the same natural or legal person to use a different trade name for medicinal products with the same active substance(s) and indications, for different strengths or route of application or pharmaceutical forms.

- A medicinal product cannot be authorized with the same name as a traditional herbal medicinal product or a homeopathic medicinal product.

With the last amendment, it has been regulated that licenses, certificates and other internationally valid documents can also be prepared as physical documents by the TİTCK. In addition, the TİTCK will announce the list of authorized medicinal products on its official website at least once a month and in the Official Gazette once a year.

15. Validity Period of License

The amendment made to the validity period of licenses states that the TİTCK will evaluate the renewal of a license five years after its issuance date, taking into account the benefit/risk balance. In this context, the license holder, pursuant to the provisions of the Regulation on the Safety of Medicines, submits the file containing all updated information on efficacy, safety and quality, including the evaluation of suspicious adverse reaction reports and periodic benefit/risk evaluation reports, and information on all variations made since the registration of the product, nine months before the expiration of the five-year period.

Once a license is renewed, it is valid indefinitely. However, there is an exception to this situation in the Regulation. The TİTCK may decide to undertake an additional five-year renewal evaluation for pharmacovigilance-related reasons, including insufficient

patient exposure to the relevant medicinal product.

In cases where five-year pharmacovigilance data for a product cannot be submitted because it has not been released to the market, the evaluation of the registration's validity is made after the current pharmacovigilance data is prepared and submitted in accordance with the relevant legislation provisions.

16. Suspension of a License

The principles regarding the suspension of a license are determined by the 22nd article of the Regulation. In the event that at least one of the following situations is detected, the TİTCK will suspend a license for a medicinal product:

- It is determined that a product's manufacturing method and the control methods used by the manufacturer are not applied as specified,
- Failure to comply with legislation relating to packaging and the patient information leaflet ("**PIL**"), not making necessary updates to the SPC and PIL,
- Not responding to the Agency's questions within the time specified,
- It is determined that there are errors in the documents submitted in the application that will affect the quality, efficacy or safety of the product, or the documents submitted lose their validity,
- No commercial batches have been placed on the market within the first 30 months of the date of registration,
- Not submitting the official documents to the Agency that shows at least one commercial batch of an authorized medicinal product manufactured in Turkey, previously put on the market, and is within the scope of QR code application has been offered in domestic or foreign markets within an uninterrupted 30 months; and the products imported to Turkey which are determined that they are not in the domestic market, or they are put on the market for medicinal products outside the scope of QR code application.
- Determining the situations that require the suspension of a license in accordance with the provisions of the Regulation on the Safety of Medicines,
- The marketing license holder's failure to place a medicinal product, which is important for the sustainability of public health and access to the drug on the market within six months of the date of request by the Agency.

The manufacturing or importation of a medicinal product, whose license is suspended for the above-mentioned reasons, is blocked. It is not possible to put medicinal

products on the market that have already been imported or produced unless the TİTCK decides to the contrary. The TİTCK makes the decision on medicinal products on the market, taking into account the reason for the suspension of the license.

However, the TİTCK may make an exception to the application of the above-mentioned issues regarding the failure to supply the medicinal product to the market within the promised period for exported medicinal products, which may cause serious public health problems if they are not ready for use or are not needed at all on Turkey's market.

Finally, it should be noted that if products whose licenses have been suspended due to the reasons stated above that exceptions can be made, are desired to be placed on the market again; in accordance with the procedures determined by the TİTCK, an application should be made to the TİTCK for the retrieval of the s license, with a commitment to put the product on the market within six months. If the TİTCK approves the application, the product license is reinstated. However, for products that are not put on the market within the promised period, actions are taken in accordance with Article 23.

17. Cancellation of a License

Another amendment made in the Regulation concerns the cancellation of licenses. The following points have been added to the reasons for cancellation listed in the previous regulation:

- The request of the license holder and the approval of the Agency, provided that there is no order of attachment or injunction notified to the Agency on the license,
- Not putting on the market within the promised period mentioned above.

In addition, applications for a co-marketed product can be made solely by presenting Module 1, or a license can be issued following the submission of a full and complete file. In cases where a license is obtained by presenting solely Module 1, revocation of the license of the product that received the license by making a full and complete application will also cause the license of the co-marketed product to be cancelled.

It should be emphasized that the import and manufacture of products whose license has been revoked cannot be carried out. The TİTCK makes the decision regarding the products currently available on the market.

18. Loss of License or Product Files

Distinct from the repealed Regulation, a new article has been added to the Regulation regarding the loss of license or product files. Accordingly, if a registration file for a medicinal product for which a registration application has been made is lost, an application for a lost registration file should be made to the TİTCK by the applicant or the license holder. A copy of the file is given to the applicant for applications whose justification is approved by the TİTCK.

In cases where the license given by the TİTCK is lost, the license holder must make a lost license application to the TİTCK with a newspaper advertisement stating that the license is lost. Following such an application, a new license is issued.

19. Liability of License Holders

Regarding the responsibility of license holders, the regulation states that if for any reason a license holder cannot put a product on the market on the date required, they must give the Agency at least 30 days' notice. In addition, because of the quality or efficacy or safety of medicinal products that are imported, exported or manufactured in Turkey under license; the TİTCK must be notified in cases of a product's suspension or cancellation of a license in other countries, its withdrawal from the market or its recall. Obligations regarding the payment of the determined fees and charges related to the products are also regulated.

In addition to the previous responsibilities, the license holder or applicant is obliged to make an application in accordance with the principles specified in the Regulation and to confirm the accuracy of the information and documents submitted to the Agency. In accordance with the Regulation, the license holder accepts all kinds of responsibility arising from the results of the information and documents submitted. The license holder is also obliged to keep the originals of all documents submitted and to submit them to the Agency upon request. It should also be noted that the fact that a medicinal product is authorized does not affect the legal and penal liability of the authorization holder.

20. Transfer of License

As it is known, it is possible to transfer the license of a medicinal product licensed by the TİTCK pursuant to the Regulation. In Article 26 of the Regulation on license transfer, the documents that must be submitted to the Agency for transfer procedures are specified. Within this scope, the documents are listed as:

- The court decision stating that it has transferred the license, the decision by

the enforcement office that the license has been sold through forced enforcement, or the contract that contains the name of the relevant medicinal product, the date and number of the license, and the names and addresses of the real or legal persons who will transfer the license and take over the license,

- A report stating that the current medicinal product file approved by the TİTCK, which is complete and updated, has been delivered to the transferee in full,
- An original or notarized copy of a diploma or graduation certificate from the Higher Education Council, showing that the person who has taken over the license can fulfill all the responsibilities expected from the license holder, and showing that they belong to one of the professions specified in Article 7 of the Regulation for those who can apply for a registration,
- In cases of the person to take over the license is a legal entity, the trade registry gazette stating the partners of the company and the duties and titles of the responsible persons,
- Documents relating to the pharmacovigilance officer within the scope of the Regulation on the Safety of Medicines,
- Documents defining the science service within the scope of the Regulation on Promotional Activities of Medicinal Products for Human Use, and the address, telephone number and REM address of this service,
- The name, surname, address, telephone number and REM address of the person who has taken over the license, together with the updated SPC, PIL, a copy of the inner and outer packaging of the medicinal product, and in the transfers made through the notary, the original of the license previously granted for the product in question; in cases where the updated SPC and PIL cannot be submitted, a fully prepared undertaking by the transferee stating that all necessary changes and updates regarding the SPC and PIL of the medicinal product will be made in line with the relevant guidelines after the registration transfer process of the medicinal product is completed, and that no sales permit application will be made without obtaining approval,
- In cases of importing medicinal products, a document issued by the licensor company showing that the real or legal person making the import is the only authorized representative for importation, licensing, and sale of the product in question in Turkey, and in the case of co-marketing, a document showing that the real

or legal person other than the authorized sole representative in Turkey has been given the co-marketing authorization, and the written approvals on common marketing of the real or legal persons who will conduct common marketing.

- In the event that a medicinal product is manufactured under a license, a document issued by the licensing company showing that the real or legal person manufactures the product is the authorized sole representative for the licensing, production and sale of the product in question in Turkey; in cases of co-marketing, the document indicating that the real or legal person other than the authorized sole representative in Turkey is granted co-marketing authorization, and written approvals of real or legal persons to co-market with,
    - In cases where the applicant is not a manufacturer of medicinal products in Turkey, the contract for contract manufacturing with a manufacturer that meets the conditions specified in the Regulation on Manufacturers of Medicinal Products for Human Use.

In addition to these, a letter of undertaking prepared by the transferee company through a notary public stating that no changes were made to the medicinal product during the transfer application must be submitted.

Furthermore, it has been regulated in Article 26 that the necessary updates to the existing product file and the actions to eliminate the deficiencies, if any, will be carried out in line with the relevant guidelines after the registration transfer, if the transferee company submits a full letter of undertaking, stating that all necessary changes and updates regarding the medicinal product will be made after the transfer is made, and it has been stated that applying for a sales permit is not possible without obtaining approval.

Another important point to underline is, in cases where there is a demand, the regulation allows the transferee company to produce products with old barcodes and place them on the market for a period of six months following the issuance of a new license, on the condition that there is a written and notarized agreement between the companies involved in the transfer of the license. Control processes for products' production notifications in this situation are carried out over the Drug Tracking System ("**DTS**"). These products can remain on the market until their expiration date, and while being imported, until the transfer to the market is stopped by the transferor company.

It is possible to import products with old barcodes for a period of six months after a

new license is issued, provided that it is agreed in writing and notarized by the transferring company. However, it is also stated in the Article 26 that these products can be offered to the market on the condition that the transferring company makes a DTS production notification, and the products are transferred to the transferring company through the DTS.

Moreover, as stated in the rest of Article 26, in cases where a licensor changes the real or legal person authorized by the licensing company for the licensing/sales/production of the product in question in Turkey, in addition to the documents listed above, a letter stating that the current license holder has returned the original license must be submitted. In cases where the current license holder submits a court decision showing that their authority is no longer valid, all the requirements in this article must be fulfilled together with the Module 1 file prepared in accordance with Annex-1 of the medicinal product, except for subparagraph (a) of the first paragraph. However, if the product in this situation is the only diagnosis or treatment option for a disease, the TİTCK may accept and conclude the transfer application for the license/permit or registration certificate without waiting for a court decision.

Finally, the TİTCK will evaluate license transfer applications within 30 days.

21. Transfer of License Application

Within the scope of Article 27 of the Regulation, it states that a real or legal person applying for a license may transfer the rights arising from the application to another real or legal person by fulfilling the conditions mentioned above regarding the transfer of the registration.

22. Obtaining a Sales Permit

The Regulation states that it is obligatory to obtain a sales permit for medicinal products that are licensed by the TİTCK and put on the market for the first time and defines the documents necessary for the sales permit. In this context, the license holder should submit the following to the TİTCK:

- The document issued by the TİTCK in the event of storage in facilities belonging to its own private or legal entity for medicinal products, for which a sales price application to the warehouse is approved,
- In other cases, the document issued by the TİTCK of the storage place,
- The document signed between the parties for the storage of the product,

- The registration certificate of the parties, together with the sales permit application.

However, the TİTCK examines all printed materials regarding the medicinal product for which the sales permit applies for necessary information.

The amendment states that there is no need to obtain a resale permit in cases where the packaging information, specifications and PIL based on the license do not change.

In addition, the situations in which the Regulation requires a sales permit include transfer of the manufacturing place from abroad to Turkey or vice versa, a change in packaging size, following a transfer process, or the suspension of a license.

23. Release to Market for Blood Products and Immunological Medicinal Products

Release to market for blood products: In Article 29 of the Regulation, it has been regulated that a license/permit holder for blood products with a sales permit, for which a permit has been applied for, or for which a registration has been applied, must apply to the TİTCK to obtain a marketing authorization for each batch of the product in addition to the issues regarding the sales permit, before placing the product on the market.

It should be emphasized that before the marketing authorization, the analyses determined according to the product for each batch of blood products or medicinal products containing blood products and for each plasma pool used in these series must be carried out in the Agency's laboratory or in a laboratory accepted by the Agency for this purpose. However, in cases where the blood product is not included as an active substance in the content of the medicinal product and the reasons for not providing the plasma pool are approved by the Agency; the analyses determined according to the product for each series of the medicinal product, without looking for plasma pool analysis, must be performed in the Agency's laboratory or in a laboratory accepted by the Agency for this purpose.

The medicinal products are allowed to be placed on the market if the amount requested to be offered for sale in order to obtain a marketing authorization for blood products or medicinal products containing blood products, and the documents and information specified in detail in the continuation of Article 29 along with the analyses are submitted to and approved by the TİTCK.

In the case of medicinal products, which are intended to be imported as bulk products and put on the market by manufacturing the finished product in Turkey, in addition to the documents required for the sales authorization for each batch of the product imported, the original document issued by the license holder and, where applicable, the licensor company, showing the country or countries where other products using plasma pools used in bulk products are licensed/manufactured, and in which countries they are sold, must be submitted to the TİTCK.

For blood products that are imported in bulk and manufactured in our country and licensed accordingly, provided that all the documents are submitted within the scope of this provision in the Regulation, and the analyses made and the relevant information and documents are approved, a permission to put the product on the market will be granted if there is a current variation commitment for the product, which is issued by the license holder and, where applicable, by the licensor company, and whose serial number is specified.

Release to market for immunological medicinal products: Article 30 of the Regulation states that for authorized immunological medicinal products with the exception of allergen products or permitted immunological medicinal products for which a license application has been made, the license/permit holder is obliged to apply to the TİTCK to obtain a marketing authorization for each batch of the product before placing it on the market.

Before marketing authorization of immunological medicinal products for which a license application has been made, analyses determined according to the product must be carried out in the Agency laboratory or in a laboratory accepted by the Agency for this purpose, as in the case of blood products.

In order to obtain a marketing authorization for immunological medicinal products for which a license application has been made or licensed, it has been regulated that the Agency must be notified of the amount requested to be placed onto the market and the documents and information specified in detail in the continuation of the article must be submitted.

Finally, the relevant batch is allowed to be placed on the market, provided that the documents submitted within the scope of the application for immunological medicinal products for which a license application has been made or licensed and the results of the analysis of the immunological medicinal products which a license

application has been made.

24. Post-Authorization Variations

With the exception of the principles stated in the Regulation on the transfer of licenses, it has been stated that after the authorization of a medicinal product, an application must be made to the TİTCK by the license holder in accordance with the provisions of the relevant regulation and guideline for all changes regarding the product.

In this regard, the Regulation on Variations in Licensed Medicinal Products for Human Use, which regulates the processes required in order to ensure the continued quality of the product, and its safe and effective supply to the market for changes to be made after the registration of medicinal products, was issued in line with current requirements in the Official Gazette dated 18 December 2021 and numbered 31693 entered into force. Likewise, the TİTCK's Department of Pharmaceutical Licensing made an announcement on 22 December 2021 and shared the Guide on Variations in Licensed Medicinal Products for Human Use and the Notification/Application Form for Variations in Licensed Medicinal Products for Human Use in accordance with Article 17 of the Following an application, the TİTCK will be able to give scientific advice to the applicant after the medicinal product is licensed, subject to the fee included in the price list.

25. Conditional Licensing (Emergency Use Approval) and Exceptional Licensing

The fourth section of the Regulation outlines the steps and requirements for exceptional and conditional licensing, setting forth the Priority Evaluation Commission as the authority that determines special situations. Regulations have been introduced regarding conditional licensing (emergency use approval) applications, their evaluation, and the term and renewal of conditional licenses. In addition, the regulations include specific requirements concerning the conditional license (emergency use approval).

Within the scope of these regulations, it is possible to submit a conditional registration application to the Agency for medicinal products that falls under at least one of the following, excluding changes related to changes in the therapeutic indications of a licensed medicinal product or the addition of new ones:

- Medicinal products intended for the treatment, prevention or medical diagnosis of life-threatening or severely disabling diseases; or

- Medicinal products that will be used in public health emergencies recognized by WHO or the European Union or accepted by the MoH.

The Regulation allows conditional licenses to be granted despite a lack of comprehensive clinical data on efficacy and safety provided that all the requirements are met if the benefit/risk balance of the medicinal product is positive, the applicant can provide comprehensive clinical data, an unmet medical need is fulfilled, or, although additional data are required, the public health benefit that the relevant medicinal product on the market provides is greater than the risk posed by its absence. The Regulation defines the aforementioned "unmet medical need" in a way that means that no medical diagnosis, disease prevention or treatment method adequately meets this need in Turkey, or even if a method does exist, the new method will provide a greater advantage in treatment for patients. The Agency must conclude this application within 90 days.

According to the Regulation, the evaluation of conditional license (emergency use approval) applications, and their duration and renewal can be realized under the following conditions.

- If it is noted that the SPC and PIL product are still insufficient in certain respects, the license's validity period will be one year and will be re-evaluated annually.
- A license holder must apply for license renewal at least 90 days before the end of the license validity period, together with an interim report on the status of specific obligations to which it is subject.
- If a license renewal application is made within the specified time period, the product can remain on the market until the Agency notifies its decision.
- When requested by the Agency, the marketing authorization holder must submit a periodic benefit/risk assessment report to the Agency immediately or at least once every six months.

In addition, it has been regulated that the obligations specific to the medicinal product for which a conditional registration application has been made will be determined by the TİTCK. Accordingly, after determining the specific requirements, it is obligatory for the marketing authorization holder to complete the ongoing studies or to carry out new studies to ensure that they fulfill the conditional authorization requirements and that the benefit/risk balance is positive for conditionally licensed products. Specific requirements may additionally be imposed for the collection of pharmacovigilance data. It is also stated in the Regulation that the TİTCK will publish

the specific obligations of the conditionally licensed product and the timeframe required for the completion of these obligations on the TİTCK's official website. In cases where all specific requirements are fulfilled, a license that is no longer subject to specific requirements is issued by the TİTCK.

According to another new addition to the Regulation, an application for an exceptional registration may be made in limited exceptional cases, provided that certain conditions, especially regarding the safety of the medicinal product, are fulfilled by the applicant. These conditions are determined as follows:

- The therapeutic indications of the medicinal product are so rare that the applicant cannot be expected to present comprehensive evidence, or
- Failure to provide detailed information in the light of existing scientific data, or
- Collecting such information goes against generally accepted medical ethics.

An exceptional license can only be granted if the applicant demonstrates for objective, verifiable reasons that the medicinal product cannot provide comprehensive data on efficacy and safety under normal conditions of use and must meet the requirements set out in Annex-1. The validity of the license depends on the annual re-evaluation of these conditions.

26. Compulsory License

Finally, as a regulation regarding compulsory registration, for products that are approved by the President to be manufactured under compulsory license due to public interest, within the scope of Article 132[1] of the Industrial Property Law, an application for a registration can be made to the TİTCK, in line with the requirements, the detailed aspects of which are determined by the TİTCK.

27. Provisional Articles

[1] **Compulsory license arising from the public interest**
ARTICLE 132- (1) If use of the invention forming the subject of patent, increase of its use, dissemination of it in general, improvement of it for a beneficial use have a great importance by the reason of public health or national security issues or if non-use of the invention forming the subject of patent or its insufficient usage in terms of either quality or quantity shall cause serious damages in terms of the economic or technological development of the country, it shall be decided by Council of Ministers upon the proposal of the relevant ministry that;
a) A compulsory license for the public interest is given,
b) There is public interest if invention is made conditionally the subject of compulsory license in the event that effective use of invention to satisfy the public interest can be realized by the patent owner.
(2) In case that a patent application or use of the invention forming the subject of patent have a great importance in terms of public health or national security, the relevant ministry shall put forward a proposal by means of taking approval of the Ministry of National Defense or the Ministry of Health.
(3) The compulsory licenses granted by the reason of public benefit may be exclusive. The compulsory license decision granted on the grounds that it has great importance in terms of national security may be limited to use of the invention by one or more businesses

The Regulation includes provisional articles on authorized and registered products (including intermediate products), transition to certified registration, application for registration for the immunological medicinal product, analysis of marketing authorization for blood products, and co-marketed medicinal products.

a. Licensed and Registered Products

The time required for the registration approval of intermediate products whose licensing process has been ongoing for a long time and are available on the market; radionuclide generators, kits, radionuclide precursor radiopharmaceuticals, which are available on the market, or which are put on the market with import permits and registration documents industrially prepared radiopharmaceuticals; blood products, and immunological medicinal products has been determined as one year. It is stated that if a transition is not completed, the permit and registration documents will be canceled, and the registration applications will be returned.

b. Certified License Transition

For medicinal products that do not have a certified license, an application for transition to a certified license must be submitted to the Agency within 60 months of the effective date of the Regulation. Lost registration applications can be made for medicinal products whose original license cannot be submitted.

Variation applications made to the Agency for medicinal products for which an application for transition to a certified license has not been made, will not be processed. In addition, there is no obligation to apply for a certified license for medicinal products whose license has been suspended.

c. Application for Transition to Immunological Medicinal Product and Analysis of Market Release for Blood Products

An immunological medicinal product registration application must be submitted to the Agency within one year of the date of entry into force of the Regulation for medicinal products, which are currently authorized as blood products, based on blood components whose active substance(s) are not obtained from human blood or plasma, but which include blood components obtained from human blood or plasma in the production process.

For these applications, it is obligatory to complete the license change process within one year of the date of application. The license suspension process will apply to

medicinal products that do not complete the license change process within this period.

d. Co-Marketed Medicinal Products

Authorization holders for medicinal products, who have made a co-marketing authorization application by submitting Module 1 before the publication date of the Regulation but who would like to make the application a full and complete file, must submit all the necessary modules to the Agency within 30 days of the publication of the Regulation.

Likewise, if the marketing authorization holders for medicinal products subject to co-marketing that were licensed by submitting Module 1 prior to the date of publication of the Regulation, wish to make their registration files full and complete, they must submit all necessary modules as updated to the Agency within six months of the publication of the Regulation.

Altuğ Özgün
Partner
altug.ozgun@cetinkaya.com

Ayça Buz
Regulatory Consultant
ayca.buz@asailacdanismanlik.com

Emre Dirik
Associate
emre.dirik@cetinkaya.com

Aysen Tahmaz
Regulatory Consultant
aysen.tahmaz@asailacdanismanlik.com

Nuri Kılıç
Healthcare Business Consultant
nuri.kilic@cetinkaya.com

CETİNKAYA

ASA