Tolga Karakan – President, Turkish Medicines and Medical Devices Agency (TITCK)

The importance and urgency of developing a vaccine during the COVID-19 pandemic is obvious

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TITCK is the regulatory agency in charge of ensuring the safety of medicines, health products, cosmetics, and personal care products in Turkey. Its recently appointed president, Dr Tolga Karakan, discusses the agency's work with the WHO, ICH and EU Commission to help Turkish patients and consumers, their experience with emergency use authorizations for COVID-19 vaccines, and the renewed support for clinical trials. In addition, he outlines the agency's priorities including the activation of the country's production capacity to grow export-oriented and bringing advanced technology and know-how to the healthcare system and industry.

Can you begin by introducing your experience with TITCK and the expectations for your tenure as head of the agency?

First of all, thank you for the opportunity. I served as the Vice President of TITCK Medical Devices and Cosmetic Products from September 2020 to May 2021. I was appointed as the President of the Turkish Medicines and Medical Devices Agency in May, 2021.

The agency aims to carry out regulatory, supervisory, and guiding activities entrusted with legal and administrative regulations and high-policy documents regarding the production, supply to the market, and consumption of pharmaceuticals, medical devices, traditional herbal, supportive and advanced treatment medicinal products and cosmetic products. I continue to contribute to the

agency’s efforts to become a people-oriented, scientifically based, value-producing, internationally leading reference agency during my term in the office. The agency significantly contributes to Turkey’s competitive position in the international market.

In addition, the agency is also involved with international platforms such as the European Union Commission working groups, Pharmaceutical Inspection Co-operation Scheme (PIC/S) and is a member of The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) that aims to harmonize worldwide regulations to ensure that medicines are effective, safe and of high quality.

As it is already known, there has been an ongoing fight against COVID-19 since 2020, defined as a pandemic by the World Health Organization (WHO). This process brought additional measures and implementations in pre-market activities such as clinical trials, inspection, and marketing authorization of medicines and in our post-market activities such as supply, and rational medicines use and promotion of them. The agency gave particular importance to the availability of products of critical importance in the fight against the pandemic and continues to do so. Additionally, the efforts to localize the materials, devices and surgical equipment used in healthcare services are supported as much as possible.

Being a year away from the year that TITCK’s second Strategic Plan (2018-2022) should be completed. What are the overall objectives that you outlined and how have your progressed?

The 2019-2023 Strategic Plan of the Agency will be one of the important milestones in moving Turkey towards the “2023 Leading Country Turkey” targets. It is known by the agency that Turkey has the infrastructure and capacity to produce pharmaceuticals, medical devices and cosmetics at world standards.

Our main goals are to activate the already existing capacity that is not used, to grow export-oriented, to take steps that will provide the advanced technology and know-how that Turkey needs. To achieve these goals, the agency continues to work together with academia, the sector and the public with a multidisciplinary approach. Corporate efforts in line with these are made in two ways. The Agency both increases its regulatory capacity and takes important steps on the supervisory side. While increasing the number of personnel, the agency also attaches great importance to the training of personnel. It is believed that the investment in institutional capacity and human resources will return as a service and contribution to public and community health.

TITCK wants to provide access to quality, effective and safe products, to ensure the rational use of medicines and to take necessary measures for the safe use of medicines and herbal products, to prioritize applications for medicines that will contribute to the health of rights and the economy of the country, to support R&D and local production in health-related fields, and to increase institutional capacity.

Performance indicators that have been created to measure, monitor and evaluate the performance targets determined for the 2021 performance program period, resource needs, and the extent to which performance targets were achieved are included in line with the objectives and targets included in the prepared 2021 performance program and the 2019-2023 strategic plan. A link is established through performance programs between the main policy objectives of the Agency and the resource framework that will implement these goals so that it could ensure the allocation and use of resources according to strategic priorities.

We live in a time when the need for COVID vaccines has put pressure on global regulators to deliver emergency authorizations. What measures has TITCK taken so far regarding the approval of vaccines?

The agency is authorized to grant Emergency Use Authorization (EUA) when the relevant data is provided for vaccines that are accepted by the World Health Organization (WHO) or the Turkish Ministry of Health within the scope of infectious diseases to be used in exceptional cases that seriously threaten public health and for which comprehensive data on efficacy, safety and quality, which are the basis for marketing authorization, are not yet available. In this context, we have been working as of December 2020. In this process, EUA applications are evaluated by a high-level commission of the agency. The commission evaluated that the benefit-risk balance of the vaccine is positive, the comprehensive clinical data can be provided by the applicant later, the unsupplied medical need is met, and the public health benefit of the availability of the relevant vaccine on the market is greater than the risk that its absence would pose, despite the need for additional data.

In addition, the EUA applicant has obligations. The obligations of the EUA applicant are to apply for a sales permit, to complete the requirements in line with the determined schedule, to submit the periodic benefit-risk assessment report every month, to state in the practitioner information text and user information text regarding the vaccine that this vaccine has received EUA until it is granted marketing authorization, that the studies on the vaccine are continuing and that the results of the studies will be re-evaluated at regular intervals. Also, to carry out work and

procedures regarding the management and reporting of adverse reactions related to vaccines receiving EAU and to present all kinds of information and documents requested by the agency in a complete and timely manner.

Turkey is one of the few countries with COVID-19 vaccine homegrown programs (three in Phase I, one in Phase II). How the previous experience approving foreign researched vaccines can help to accelerate the review of these programs?

The importance and urgency of developing a vaccine during the COVID-19 pandemic is obvious. During the COVID-19 vaccine development process, authorities including the WHO, EMA and US FDA provided various exceptions due to the “Public Health Emergency Situation”. These exceptions are also valid in Turkey. TITCK closely follows all scientific developments and conducts guiding activities for groups developing vaccines in parallel with international practices. The Agency has prepared a “Table of Requirements for the Transition of Viral Vaccine Candidates to Clinical Trials”, which contains very detailed information to guide the research groups that conduct and will conduct the COVID-19 vaccine study and shared with all stakeholders.

In addition, it guided the vaccine development groups regarding the studies that should be completed before transitioning to the clinical trial phase by publishing “The Guidelines for Non-Clinical Evaluation of Human Vaccines.” The WHO were also consulted during the publication of all these guidelines. The publication of regulatory and guiding documents in the early period and the establishment of scientific commissions to carry out these processes reveal the knowledge on this subject.

The Sinovac and Biontech/Pfizer vaccines, whose Phase III research is conducted in Turkey, have been approved for use in Turkey. These vaccines are also included in the emergency use list by the WHO. This shows that Turkey’s evaluation processes are in line with internationally accepted standards.

Following and directing the vaccine development processes from the very beginning and including Turkey in international clinical trials provide many advantages in terms of evaluation processes. In this process, the experience gained in the existing knowledge and evaluation processes can be transferred to local vaccine development programs. This naturally accelerates the evaluation processes as of the current period.

The new generation of genetic vaccines (RNA-based) has put a spotlight on breakthrough technology for medicine. Since no regulator had previous experience with them, what are the lessons you learned and how do you view their potential for the future?

MRNA vaccines are a new type of vaccine that protects against infectious diseases. The effect mechanism of many vaccines is based on the administration of weakened or inactivated viruses to trigger an immune response in our body. mRNA vaccines are also intended to stimulate the production of antibodies to bind to potential pathogens. This mRNA sequence is translated by the host cell to produce the encoded antigens upon administration of the vaccine. These antigens stimulate the body's immune system, triggering the production of antibodies against the pathogen. In other words, the mechanism of mRNA vaccines is based on the production of the protein (sometimes just a piece of protein) that triggers the immune response in the host cells. This immune response is thought to be similar to the immune response against the real virus. The results of the studies show that the immune response created by mRNA vaccines is at very high levels.

The production process of these vaccines is fast and the production capacity is high. In addition, it appears that mRNA vaccines can be adapted more quickly to new situations (such as variants). This leads to the high potential of mRNA vaccines for the future. However, it should be kept in mind that mRNA vaccines are a new type of vaccine and long-term data should be carefully evaluated due to the complexity of the production technology.

In Turkey, there is currently no locally developed mRNA-based vaccine candidate that has applied to TITCK for clinical trials. However, clinical studies of foreign-sourced mRNA vaccines were carried out in Turkey and evaluated. Evaluation of these vaccines continues to be made in terms of their requirements for this type of vaccine in line with published guidelines.

Turkey's Vision 2023 is focused on global competitiveness for the pharma and biopharma industry. A good level of regulatory science is a critical point, especially in the nurturing and development of clinical trials. What role will TITCK play in incentivizing clinical trials?

One of the main policies of Turkey in its medium and long-term development plans is to increase its competitiveness in the global pharmaceutical market and to occupy a higher position in the value chain. In line with this policy, "to become the leading country in the region in the field of

clinical trials” is one of its main goals. Turkey aims to increase its share from global clinical trials both in numbers and economically. In this context, Turkey has taken several initiatives in recent years, including the legal regulations it has implemented to improve the clinical trial environment. Turkey, with a solid legislative infrastructure following European Union standards, has become a strong candidate for multinational clinical trials.

As it is already known, the regulatory and supervisory authority in Turkey in the field of clinical trials is TITCK. The biggest task of regulatory authorities is to reveal regulations following international norms and to complete the evaluation processes transparently, consistently and as soon as possible.

Clinical trials in Turkey is an area that has been regulated for many years and there is a lot of experience in this field. Turkey has a legal regulatory environment that is compatible with the European Union and ICH regulations and adapts to new trends developing in the world. Consistency and functionality of legal regulations and international standards create an environment of trust in clinical trials in Turkey.

At the same time, TITCK has made great progress in recent years in terms of structural changes and improvements and evaluation times. While the average application evaluation period was 100 days in 2016, this period decreased to 26 days in 2020.

It is extremely important for the authorities to carry out the regulatory and supervisory functions, which are their main duties, as well as to perform the guiding activities. To develop the clinical trials ecosystem, TITCK carries out activities on different topics in cooperation with the relevant stakeholders, and this situation reflects positively on the ecosystem.

For example, activities are carried out on subjects such as shortening central contracting processes, increasing awareness of clinical trials in the public and health professionals, transparency in clinical trials, developing information systems in clinical trials, increasing the scope of R&D incentives and the number of competent researchers, providing researcher incentives and disseminating clinical trials training.

Is the level of patient data available and the digitalization of the healthcare system robust enough to have that data used for market approval at some point?

Despite the ongoing difficulties due to the COVID-19 pandemic, which affected the whole world in 2020, necessary studies were carried out to ensure that medical products for human use, which are

important for public health, are supplied to the market in a quality, effective and safe manner. This challenging process has once again shown how effective countries should be in pharmaceuticals and vaccine development processes. In addition, the need for products has increased in product groups within the scope of many medicines, biological and medical products, which are important for public health, especially personal protective equipment and medical masks in the world and Turkey due to the COVID-19 pandemic, and accordingly, new regulations have to be implemented.

The Pharmaceutical Track and Trace System (ITS) is an adapted form of the worldwide tracking and monitoring system to the pharmaceutical industry. With this system, it is possible to determine the position of pharmaceutical (medicines for human use, traditional herbal medicinal products and foods for special medical purposes) in the supply and distribution processes. Each movement of any pharmaceuticals from the production or import to the sale (human medicinal products, traditional herbal medicinal products and special medical purpose foods) can be monitored thanks to the marked QR code. The Pharmaceutical Track and Trace System Project, an innovative breakthrough, is followed with interest by many countries and has been introduced to many countries in recent years. The most important purpose of the Pharmaceutical Track and Trace System is to ensure patient safety. It is ensured that the unsafe environment does not reoccur, and that the medicines reach the patients safely and that the trust of the patients in the medicines is maintained by detecting patient safety violations as a result of examining the data collected by the system, which has an important role in improving and protecting patient safety.

On the other hand, the Product Tracking System (UTS) is an e-Government application that provides citizen-oriented services and has hundreds of thousands of users and is a national recording and monitoring system introduced in 2017, where all medical devices and cosmetic products manufactured or imported in our country are recorded, and medical devices can be tracked from the production line to the place where they are used and the patient. In UTS, individual tracking of medical devices can be provided in addition to the company, documents and product records regarding medical devices and cosmetic products. There are approximately 4.5 million medical devices and 300 thousand different cosmetic products registered in Turkey. UTS has been developed as a good practice example for the registration of medical devices, movement processes between institutions, organizations, market surveillance and inspection activities, clinical engineering processes, and citizen-oriented services and systems, which have an important place in the UTS mobile application.

As you mentioned, TITCK has joined the International Council for Harmonization (ICH), verifying that Turkey meets international standards for regulatory aspects of medicines. What are you expecting to leverage from this?

TITCK, as a member with observer status on 7 June 2018, was accepted as a member of the ICH on 27 May 2020, an organization that aims to harmonize worldwide regulations to ensure that medicines are effective, safe and of high quality.

ICH membership indicates TITCK's and sector's commitment to the highest global standards for quality, efficacy and safety in pharmaceuticals. In addition, this membership has enabled TITCK to have a worldwide voice in the field of pharmaceuticals and has made it one of the countries that will determine the rules in this regard. Currently, TITCK experts take part in the development expert groups of many ICH guidelines and participate in these studies.

In addition, TITCK develops bilateral relations such as information exchange, training and mutual recognition practices as part of a worldwide network that has a voice in this matter.

ICH membership reinforces the confidence in Turkey in terms of the pharmaceutical industry and reveals the quality of TITCK's evaluation processes. This supports both the foreign industry's investment in the country and the domestic industry's exports.

This year marks the 10th anniversary of the creation of TITCK. What are your priorities and what sort of leadership can the agency have across Europe and the Middle East?

Since its first establishment, the agency has continued its efforts to become a human-oriented, scientifically based, value-producing, internationally leading reference institution. In addition, the agency operates to have a voice in international platforms by being involved in international platforms such as the European Union Commission working groups, Pharmaceutical Inspection Co-operation Scheme (PIC/S). There is an ongoing fight against the COVID-19 pandemic. It is seen once again that how important strategic management in this challenging process is. The Agency has given particular importance to the availability of products of critical importance in the fight against the pandemic and has focused on studies in this regard. The Agency has continued the inspections of product groups such as medical masks and disinfectants effectively and intensively during this process. The Agency is on the way to increase public, sector and academia cooperation by supporting our local production. Thus, we continue our efforts to make Turkey one of the leading countries in the global market.

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