New Legislation on Manufacturing Plants of Human Medicinal Products

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I - Introduction

Following the enforcement of the new Communiqué on Pricing of Human Medicinal Products last September, the Ministry of Health ("Ministry") rolled up its sleeves for a new regulation concerning human medicinal products: The Regulation on Manufacturing Plants of Human Medicinal Products ("Regulation").

With an eye to regulate human medicinal product manufacturing and importing in line with internationally acknowledged standards, the Ministry has published the Regulation on the Official Gazette of October 21st, 2017.

Upon the publication of the Regulation, the predecessor Regulation on Human Medicinal Products Manufactories (published in 2013 - "Abolished Regulation") has been abrogated.

II – New Definitions

Somewhere down the list of definitions under Article 4 of the Regulation are definitions of "primarily packaging" and "secondary packaging" which have been introduced. With this division made on the packaging definition, procedure on interior packaging (i.e. packaging which directly interacts with the human medicinal product) of human medicinal products will be deemed as "primary packaging", whereas procedures such as replacement of the interior packaging into exterior packaging, packaging changing, printing, barcoding/patterning, inserting banderole/label, adding or changing prospectus/operating instructions will be considered as "secondary packaging". Both primary and secondary packaging will be accepted as part of the "manufacturing" process.

III – License Holder's Responsibilities

The responsibilities of the holders of the license for manufacturing plants are governed under Article 8 of the Regulation. The Ministry has added certain provisions to the responsibility list which seem to bring a strict monitoring liability to license holders.

For instance, license holders will be responsible to assign a manager within 30 days after the resignation of the current manager and notify the Ministry accordingly. Also, license holders will have to hold the documentation proving that their manufacturers, importers or distributors of active agents are duly registered in their countries. License holders, in this respect, will have to confirm safety and quality of active agents and inactive ingredients that they use and ensure necessary control over human medicinal products as well as active agents during all stages of manufacturing.

Article 8 also brings a notification responsibility to license holders if they come to the conclusion or even suspect that the products are counterfeit.

IV - Audit

Article 10 contains detailed arrangements on audit of human medicinal product manufacturing sites. As per the Article, these sites, as well as laboratories and importers that provide contractual analysis services for human medicinal products, are subject to routine inspections within the program which is the result of the Turkish Drug and Medical Device Institution's ("Institution") risk-based evaluation. These audits can be done without notice when necessary.

If following the audits, the sites are determined to be incompatible with the applicable legislation; the Institution can grant the relevant site a period of time sufficient to repair the deficiencies. As of the expiration of this period, if it is deemed necessary, new on-site audits can be carried out to determine whether the deficiencies are repaired.

V –Imports

Article 13 of the Regulation sets forth principles on the imports of human medicinal products. According to thearticle, importers should be able to submit their Good Manufacturing Practices Certificate and/or production permit to the Institution. If they do not possess a Good Manufacturing Practices Certificate they should apply to the Institution in line with the guidelines of the Institution.

Article 13 also brings certain responsibilities to importers. As per the Article importers will have to:

(i) Supply human medicinal products from the plants approved by the competent authority of the country of manufacture. If they import clinical research products, they will have to supply these products from manufacturers that are approved and the products of which have been notified to competent authority.

(ii) Ensure that all batches of imported human medicinal products are released into the Turkish market after being tested and controlled within the frame of product license file/specifications.

Apart from the foregoing, license holders will be obliged to (i) provide the manufacturer with samples at the sufficient amount to conduct at least 2 analytical controls or at the amount approved by the Institution and (ii) preserve expired products for at least 1 year after their expiration date.

VI - Active Agents and Inactive Ingredients

Principles on active agents and inactive ingredients are regulated under Article 14 of the Regulation. According to Article 14 (2), permit/license holders should confirm that their manufacturers and distributors of active agents are in compliance with the principles of Good Manufacturing Practices and Good Delivery Practices, by way of auditing the manufacturing and distribution sites of these manufacturers and distributors.

On a side note, as per Article 32 of the Regulation, Article 14 (2) will be effective one year after the date of publication of the Regulation (*i.e. October 21st, 2018*).

VII – Internal Audit

Article 24 of the Regulation brings an internal audit obligation to manufacturers. Internal audit is deemed necessary for the purposes of taking required corrective actions within scope of Good Manufacturing Practices. Manufacturers will also have to take records of these internal audits..

VIII - Administrative Sanctions

Article 27 of the Regulation provides a more detailed regulation on sanctions to be imposed on license/permit holders as well as managers. While the Ministry maintains its suspension and withdrawal authorization, certain changes made in the Article sheds light to aftermath of suspension/withdrawal.

As per Article 27 (4), the Institution will determine how to proceed with products distributed before the suspension or withdrawal by manufacturers whose licenses are suspended or withdrawn.

If breaches which require suspension of production permit are not remedied within a year, production permit as to related operations, if all operations are suspended production permit for the manufactory, will be withdrawn.

As to sanctions against the managers, Article 27 (7) regulates that the following audits at the manufactory, in case it is determined that the manager was absent without duly excuse three times during its duty, his/her management permit will be withdrawn and the manufactory will be obliged to appoint a new manager and notify the Institution in line with the Regulation.

IV – Transition Period

Importers wishing to conduct only batch release operations are obliged to apply to the Ministry and obtain a permit within one year as of publication of the Regulation.

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