A new policy regarding the registration and use of bio-similar pharmaceuticals in Israel

June 8, 2014

On April 2014, the Israeli Ministry of Health ("MoH") issued a new work procedure, no. 127, which provides for more structured and detailed policy and procedures for the registration and use of bio-similar pharmaceuticals in Israel ("the Work Procedure").

Up until the issuance of Work Procedure 127, the MoH operated through an internal guideline, according to which bio-similar pharmaceuticals could be registered with the MoH if they had been previously registered with the European Medicines Agency (EMA) via the “Bio-Similar” route, or with the US Federal Drug Administration (FDA) via the “Follow on Protein Products” route. Each application was to be considered on a case-by-case basis.

At the outset, the Work Procedure notes that bio-similar pharmaceuticals are pharmaceuticals that comprise an active ingredient that is produced from a living organism. The Work Procedure acknowledges that in view of their complexity and manner of manufacture, biological active ingredients are similar but not identical, and, accordingly, notes that the rules that apply to chemical generics do not apply to bio-similars.

The Work Procedure defines a Bio-Similar Pharmaceutical as a biological pharmaceutical comprising a biological active ingredient that is similar to the active ingredient of an original biological pharmaceutical ("Reference Medicinal Product"). A Bio-Similar Pharmaceutical should be similar to the Reference Medicinal Product in aspects of quality characteristics, biological activity, safety and efficacy, as established in comparative tests.

In general, according to the Work Procedure, the MoH adopts EMA policies in the relevant issues at hand, relating to Bio-Similar Pharmaceuticals, customized to the need of the State of Israel.

Conditions for the registration of a Bio-Similar Pharmaceutical

The Work Procedure provides two accumulative conditions that must be fulfilled in order to register a Bio-Similar Pharmaceutical in Israel:

(i) The Bio-Similar Pharmaceutical must be registered with the EMA or the FDA.
(ii) The registration file must include data that proves that the Bio-Similar Pharmaceutical is similar to the Reference Medicinal Product and that there is no significant difference in aspects of quality, safety and efficacy;

As a general rule, the registration of a Bio-Similar Pharmaceutical will not be allowed if the Reference Medicinal Product is not registered in Israel. However, in certain exceptional cases, in which a national
clinical need exists, the registration of a Bio-Similar Pharmaceutical may be considered even if the Reference Medicinal Product is not registered in Israel, provided that the Bio-Similar Pharmaceutical was approved by one of the recognized regulatory authorities (the FDA or the EMA). Such exceptional cases will be brought before an advisory committee for bio-similars that was established by the Work Procedure and will be eventually decided by the management of the MoH.

**The Choice between Reference Medicinal Products and Bio-Similar Pharmaceuticals**

The Work Procedure allows a medical institution to determine whether a treatment will make use of the Reference Medicinal Product or the Bio-Similar Pharmaceutical. The commercial name of the Bio-Similar Pharmaceutical must, therefore, appear in the prescriptions issued by the medical institution.

Once such treatment is commenced, no automatic substitution between the pharmaceuticals may be made.

Nevertheless, the Procedure enables a certain leeway in this regard, allowing the recognition (by way of registration in the Register) of the interchangeability of a specific Reference Medicinal Products by a specific Bio-Similar Pharmaceutical. Such a recognition may be made either upon registration of the Bio-Similar Pharmaceutical or later during the period of its registration. The approval of interchangeability will be made based on the recommendation of a bio-similar advisory committee, convened ad hoc.

**Labeling of a Bio-Similar Pharmaceutical**

The issue of labeling a Bio-Similar Pharmaceutical is also addressed in the Work Procedure, according to which a Bio-Similar Pharmaceutical must be labeled in a clearly identifying manner, so as to distinguish it from other biological pharmaceuticals.

In addition, the commercial name followed by the active ingredient name in parenthesis should be indicated on the label, on the leaflet, in the drug registry, and in the drug information databases.

**Indications for Bio-Similar Pharmaceuticals**

Specific provisions of the Work Procedure also refer to the approval of indications for a Bio-Similar Pharmaceutical.

Indications of a Bio-Similar Pharmaceutical will be approved only if:

(i) They are approved also for the Reference Medicinal Product;
(ii) They were tested in clinical trials of the Bio-Similar Pharmaceutical;
(iii) They were approved (for the Bio-Similar Pharmaceutical) by the EMA and/or FDA.

Extrapolations from indications for a Reference Medicinal Product, being an exception to the foregoing general rule, will be allowed only if the biological mechanism of action of the Bio-Similar Pharmaceuticals and of the Reference Medicinal Product are identical.

**Pharmacovigilance**

The Work Procedure notes that due to the lack of experience in using Bio-Similar Pharmaceuticals, great importance is given to pharmacovigilance. Therefore, a Risk Management Plan or a Risk Evaluation and Mitigation Strategy has to be presented as part of the application for the registration of a Bio-Similar Pharmaceutical.

The Registrants are expected to proactively report adverse effects.
Issues not addressed in the Work Procedure

Among the issues that attracted professional public attention, and which are missing from the Work Procedure, we highlight the following:

A. **Children:** The Work Procedure does not address the indication of Bio-Similar Pharmaceuticals to children. No specific rules were established.

B. **Informed Consent of Patient:** The issue of informed consent has been given considerable attention worldwide. As noted, for example, that “*it is important that patients have a thorough conversation with their prescribing doctor about all the available therapeutic options, their safety, benefits and risks, and the differences between the medicines, before coming to a decision concerning treatment*.” This issue is also not addressed by the Work Procedure but additional rules may be prescribed in due course.

C. **Ongoing Assessment by the MoH:** As noted, companies are expected to proactively report side effects of Bio-Similar Pharmaceuticals. No reporting requirements were imposed on the health management organizations (referred to locally as “Sick Funds”), that cumulatively concentrate a major part of the healthcare market, and a procedure of post registration assessment and monitoring of future technological developments by the MoH was likewise not established.

**Conclusion**

The ramifications of the Work Procedure on the registration of Bio-Similar Pharmaceuticals and/or Reference Medicinal Product are yet to be studied and examined. Generally, the Work Procedure reflects an attempt to strike a careful balance between considerations of public health, expenditure and of patients’ safety and health, taking into consideration the special biological and medicinal features of Bio-Similar Pharmaceuticals. Time will tell whether the goal was achieved.

Chen Ben Dori - Alkan
Adv., Partner

Eran Bareket
Adv., Senior Partner

---

1 Under the name: “Policy regarding Registration and Use Conditions of Bio-Similar Pharmaceuticals”.

2 The commencement date of the Work Procedure is its publication date; namely, April 1st, 2014.

3 The internal guideline was published in the form of a letter to the pharmacists-in-charge of registration owners, dated March 31st, 2009.

4 Under certain conditions as follows: (1) all data filed with the EMA or FDA should be filed together with the registration application; (2) the original pharmaceutical is registered in the Israeli Registry of Pharmaceuticals, and contains the identical active substance of the pharmaceutical applied for registration.

5 Because of their great complexity and their manner of manufacture, some active biological ingredients are similar but not identical.

6 In any event, the MoH may request additional information at its own discretion.

7 This will also enable the monitoring of adverse effects.

8 The pharmaceutical company is required to comply in this respect with the “Report on Adverse Effects and Medicinal Information” work procedure of the Pharmacist Department dated June 1998.

9 “What you need to know about Biosimilar Medicinal Products” (European Commission), section 20. Available at:
These newsletters are provided for general information only. It is not intended as legal advice or opinion and cannot be relied upon as such.