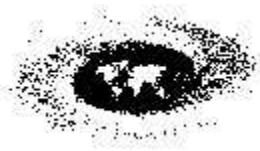

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Mexico: Polymorph Applications: The Mexican Approach
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In the summer of 1998, Abbot Laboratories was forced to remove a first crystalline form of its medicament ritonavir, a peptidomimetic drug used to treat HIV-1 infection, in favor of a second molecular form, or polymorph, which had different dissolution properties. The first molecule was originally formulated as an encapsulated solution in ethanol/water. After some time, this compound began to precipitate inside the capsule and therefore affected the oral bioavailability of the drug. Therefore, it was considered that the dissolution properties were not adequate and the medicament was not considered effective anymore. Therefore, Abbot was forced to look for a more favorable vehicle for this newly formed molecule, the more stable polymorph that showed a different solubility from the marketed product.

The above is only one of a lot of examples showing the utmost importance that polymorphs have in the pharmaceutical industry.

It is known that Active Pharmaceutical Ingredients (APIs) exist in a huge variety of solid forms, such as polymorphs, pseudopolymorphs, salts, cocrystals, and amorphous solids.

A polymorph is a solid crystalline form of a given compound resulting from at least two possible molecular arrangements of the compound in solid state. Two different polymorphs of the same API show differences in appearance, solubility, melting point, density, dissolution, etc, properties which affect the bioavailability, stability, and even safety and efficacy of the API.

The choice of a particular crystalline form over another for developing and manufacturing medicaments requires intense and prolonged experimentation, since several elements such as clinical trials, production costs analyses, bioavailability, stability, dissolution rates assessments, etc. are involved.

Therefore, the protection of a polymorph, which derives from an original crystalline form, by means of a patent is essential to provide it of a suitable protection since the scope of the parental API patent does not cover the derived polymorph. Moreover, this second generation patents form part of a strategy directed to enlarge patent protection of the product.

In Mexico, as it occurs in USA and Europe, patent applications claiming polymorphs are often patentable. However, the prosecution of these applications will present obstacles most of the time, since objections such as lack of inventive activity and/or support in the specification are typically issued during the substantive examination.

Patent applications claiming alternate crystalline forms of a known compound are considered as selection patents in Mexico. Thus, if the specification of a patent application does not indicate the technical advantages of the polymorph over the prior art compound and/or if the corresponding examples supporting said alleged advantages are not included, the application will surely be objected.

In most cases, the aforementioned objections could be overcome by providing the corresponding experimental data, which indicate the technical advantages of the alternate crystalline form over the prior art compound, such as improved solubility or better stability. Otherwise, in the absence of such data, the prosecution could turn into a long and complicated process because examiners are usually reluctant to grant a selection patent based only on arguments, since there is not evidence that supports the alleged technical advantage of the invention. In this particular respect, it is important to point out that such experimental data will not be able to be considered as a part of the specification, but that they will constitute an important aid in trying to demonstrate that the invention does involve an inventive step.

Additionally, it is worthwhile to mention that a very important issue is to try to avoid clarity objections. Although in general terms the clarity objections are easier to overcome than inventive activity or support objections, it is always preferable to correctly characterize the polymorph by techniques such as X-ray powder diffraction, Infrared Spectroscopy, Differential

Scanning Calorimetry, melting point, etc. in order not to receive said clarity objections,

In conclusion, it can be said that one of the most important aspects that applicants should carefully observe when drafting a polymorph application is to indicate all the technical elements permitting to clearly differentiate the technical advantages of the polymorph from the closest prior art compound and, if possible, to include comparative examples that support said technical advantages.

If for any reason the above is not possible, the application must contain a "sufficient" disclosure that provides technical support to experimental data and/or the arguments during the substantive examination procedure. In some cases, the difficulties to overcome an inventive activity objection fall in the lack of disclosure that supports said experimental evidence and/or the argumentation. If at least some of these measures are considered when drafting a polymorph application, the prosecution of the case will be less handicapped.

Moreover, a polymorph application that is suitably drafted will result in a granted patent that is able to stand up in case of a litigation process.

The content of this article is intended to provide a general guide to the subject matter. Specialist advice should be sought about your specific circumstances.

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