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***MANAGING INTELLECTUAL PROPERTY, SEPTEMBER 2005***

For the past couple of years the world has battled with the idea of pharmaceutical generics. The reason is the expiration of a great number of active ingredient patents in force during the 1970s and 1980s, giving rise to a market for drugs that are copies of the formerly patented or so-called innovative products, generally known by the same of generics.

Generic drugs have become an alternative to innovative drugs, in particular those subject to patent protection that has expired. However, pharmaceuticals is an industry that differs greatly from others, considering that manufacturers of generic products cannot just make their own generic version of an innovative product to be so freely launched into the market. Drugs are remedies to protect human health and are thus the subject of strict legal control.

Developers of new drugs or substances are usually compelled to submit technical information in a dossier so that the government can approve the new discovery and grant marketing authorization or registration. The key purpose of this requirement is to ensure that such discoveries meet efficacy and safety standards. Accordingly, applicants are required to provide the results of investigations or tests of different kinds, including pharmacological, toxicological and clinical tests.

The efficacy and safety process is generally divided into phases including the pre-clinical phase, which determines the toxicity and pharmacological effect of the product, and the clinical phase, which tests the product in the human body. In countries or regions such as the US, Japan and the EU, the approval process for new drugs is complex, which is expensive and time consuming. Not surprisingly, the innovative industry has vehemently protested, as the timing issue has led to patent term reduction, and is regarded as an obstacle or barrier to patent rights.

Another sensitive issue is what producers or sellers of generic drugs need to show to obtain the authorization and right to sell. At first glance, it appears that they are required to perform their own clinical tests so that regulators have no doubt that the product in question can be prescribed to patients. However, generic producers complain that it is unnecessary to make them submit full

investigative analysis when the innovator has already produced the tests. Generic drugs copy the active ingredient of the innovator. The innovator's original findings become a reference for the generic maker for equivalency and interchangeability effects, thus making it possible for physicians to prescribe or dispense them. Accordingly, the government should gather every proof needed from generic makers so that drugs subject to approval meet appropriate quality standards. For example, the regulatory authority should require information showing that the generic drugs have the same composition and method of manufacture as the innovator, that their ingredients have been controlled, and that the product is rather stable. However, anything concerning clinical trials or other investigative evidence indicating safety or efficacy should be exempted or, if still required, should be freely taken from the dossier of the innovator. Obviously, innovators are not comfortable with the latter as they consider data in dossiers to be confidential.

Tensions have become evident as innovators have pushed for extended patent terms and for stricter rules during the marketing approval process for generics, including safety and efficacy and data exclusivity. Likewise, innovators have stressed the need for better communication between the patent and healthcare authorities. On the other hand, generic makers have claimed that approval requirements should become more flexible, while recognizing their right to begin experimentation before patent expiration.

National governments have adopted a number of measures to tackle these problems. For example, the US solution to the marketing authorization issue has been the subject of healthcare legislation reform and in particular the implementation of the so-called Hatch-Waxman Act.

As a result of Hatch-Waxman, generic drugs makers can obtain drug approvals by filing an abbreviated new drug application (ANDA). Not filing the full safety and efficacy information as required for a new drug application (NDA), companies seeking ANDAs are entitled to submit bio-equivalence data between the innovator and the generic sought to be marketed. European countries have adopted similar laws. For example, Spain has an abridged proceeding by which an applicant seeking authorization for a generic drug proves safety and efficacy by pointing out documentation in the dossier of the relevant innovator, and then showing that the generic and innovative are bio-equivalent.

## THE SITUATION IN MEXICO

Mexico requires government sanitary approval - a registration - for the lawful sale of pharmaceutical products. Applicants for approval need to show that the product meets efficacy and safety profiles. In addition, the Regulations to the Health Law on Health Investigation of 1987 impose on the applicants an obligation to perform investigative or clinic analysis to show safety and efficacy. The requirement is not for every drug, but exclusively for those medicines or biological products for human use “for which there is no previous experience in the country, that have not been registered and therefore, that have not been distributed for commercial purposes as well as medicaments that have been registered and approved for sale, when investigation is being made for different modalities, indications, doses or via administrations than those approved already". In keeping with this, health authorities in charge of marketing approvals ask from applicants of products "with no previous experience" investigative analyses divided into pre-clinical and clinical phases.

The regulatory authorities also require that products comply with the pharmacology of Mexico, which among other things, refers to a certificate of good manufacturing practices, certificate of free sale, quantitative and qualitative formulas, ingredient specifications and method of analysis, certificate of analysis of supplier of the ingredients and the manufacturer of the end product, protocol of manufacture, protocol of stability data and proof of stability, chromatograms and spectrograms and fulfillment of government stability standards. For products "with previous experience" the government only requires the pharmacology.

The new generics system immediately raised a number of questions and concerns dealing with quality, efficacy and safety considerations and how these concepts would be affected in connection with the marketing approval and product registration of these types of drugs.

In response, on May 7 1997, the Congress of Mexico passed a bill of amendments to the Health Law enhancing streamlined rules for generic pharmaceuticals. This was made in response to the WHO's initiatives (see box). Before the amendment, the manufacture and distribution of generics were restricted and confined to specific areas in the government and public health sectors. But a key provision, article 225, of the amended law established that pharmaceutical products should be called by a generic name, the use of which was regarded as mandatory, as well as a distinctive name, the use of which was

voluntary.
While the bill was under discussion in Congress, research and development laboratories objected to article 225 because it failed to define when a drug could be labelled using the generic name — in other words, when a drug can be considered generic. The trouble is that even if two drugs contain the same active ingredient, the drugs' composition and quality might not be identical. The two drugs could thus produce a different effect.
The main flaw of article 225 was that it did not impose any sort of restrictions in connection with the use of INNs — the official international generic name as determined by the WHO — ensuring that every product called by a particular name is bio-equivalent to the original or innovator. If bio-equivalency were required, the generic product, to be regarded an equivalent substitute of the innovator, would have to act with the same degree and the same power and strength as the innovator in the human body.
The government responded positively to industry's arguments, and implemented a new set of regulations, the Regulations for Health Expenditures. These 1998 regulations introduced a definition of interchangeable generic drug (GI), as a pharmaceutical speciality that is equal — same active ingredient, pharmaceutical form, concentration, potency, means of administration and specifications — and equivalent—same dissolution profile and bio-disponibility — to the innovator drug, and that is solely identified under generic name. Later, between 1998 and 1999, the government published a sequence of standards that determine the different proofs for demonstrating interchangeability of generic drugs and the requirements that entities carrying the proofs shall comply with.
The regulations and standards required that government authorities test — or authorized third parties to perform tests — and approve interchangeable generic drugs to ensure that they are equivalent to the original drug. After approval, the drug is registered in the Catalogue of Generic Interchangeable Drugs, under the appropriate INN. Labels affixed on the products must include, *inter alia,* the drug’s generic name and the reference GI. As interchangeable drugs were sold as generics it would not be possible to use distinctive names.
Under the framework of the Health Law and Expenditures Regulations, laboratories making generics could choose between having an inscription in the Catalogue for a non-branded bio-equivalent product or selling an untested generic with a brand.

In accordance with the Health Law and the Regulations for Health Expenditures, generics are exclusively those fulfilling the GI requirements. The provisions state that laboratories are entitled to one registration per product, unless they make a second addressed to the generics market. The Law does not include a definition of the word generics, but the Regulations have made it clear that for the purposes of the Law of Health generics are those exclusively fulfilling the requirements of interchangeable generics.
The healthcare system has struggled with the odd situation triggered from the fact that innovator drugs started to coexist with generics tested for bio-equivalency as well as drugs untested for that same reason. In other words, the government did not impose bio-equivalency as a requirement for all generic products to comply with and rather contributed to the situation whereby applicants could voluntarily choose between testing or not to obtain sale approval. It is hard to know why the government made divisions by creating the GI definition. In any event, by doing that, the government dug a hole that generic producers and distributors used for escaping from the bio-equivalency rule.

## THE 2005 AMENDMENT

Problems generated by the hybrid generic system have been enormous. Similars and other types of untested drugs suddenly started invading the pharmaceutical market. Generic drug makers were lawfully allowed to produce low-quality and perhaps unsafe medicines to be legally sold in the Mexican market and abroad. Online and other media became the usual means of distribution. The US Food and Drug Administration and other equivalent foreign compliance authorities complained about the new practice, but could not do much because under treaties or other international instruments there were no rules addressing the issue of generics regulatory compliance. The health secretary recognized the issues and reacted by lobbying for modifications to the Health Law to solve a very sensitive problem. As a result of the lobbying efforts, Congress discussed and passed a bill of amendments, which the president signed into law on December 14 2004, and which was published in the Gazette of the federal government of February 24 2005.

The amendment deals with product registration of drugs and other supplies for health. Registration was formerly indefinite and was reduced to a five-year term that can be renewed. The key aspect of the reform is that renewal implies the need to prove safety and efficacy. The health secretariat is responsible for rendering regulations to determine the requirements, tests and other proofs that medicines must comply with for renewal purposes. The provision targets every single product registered, including innovator, GIs and other generics. However, from a practical standpoint, the government's aim is to regulate the number of registrations covering untested medicines.

Regulations have not yet been published — the government is still working on them. However, it can be anticipated that bio-equivalency shall be required without exception so that all products can be interchanged when referenced with an innovator. Likewise, registrants will have to demonstrate that the products continue to comply with pharmacology norms and procedures.

The step that the Mexican government has taken with this amendment is certainly encouraging, as it signifies the phasing out of the similars industry. Implementation of a regulatory system is under discussion, including determination of government fees, verification powers of health authorities and the framework of time for the submission of renewals and the government's response. There are concerns raised by industry that the renewal process will not be completed for five years. However, the main concern will be re-defining the concept of generics now sub-divided into interchangeable generics that cannot use a trade mark and generics that can use a trade mark. Under a GI system, brand generics that are renewed would be required to stop using trade marks, and that could be a tough measure. If every registered generic product will now have to be tested for renewal, it seems that the GI regime will become more irrelevant than when it was implemented. Obviously, the government will have to deal with this issue in the future so that the generic system is strong and consistent.

The amendment looks quite positive and the expectation is that it will ultimately contribute to the aim that medicines made or sold in Mexico are safe and of a quality at least comparable to innovator drugs.

*THE NOTION OF BIO-EQUIVALENCY*

*THE EQUIVALENCY QUESTION HAS BECOME A HINDRANCE FOR GENERICS. AS A MATTER OF PRINCIPLE, INNOVATOR DRUGS ARE REQUIRED TO ACT AS A POINT OF REFERENCE FOR GENERICS WHEN IT COMES TO TESTING PRODUCTS FOR MARKETING APPROVAL. IT HAS BEEN STATED THAT INNOVATOR PRODUCTS CAN BE INTERCHANGED BY GENERICS WHEN THE LATTER SHOW THERAPEUTIC BIO-EQUIVALENCY. THAT CAN ONLY BE ACHIEVED IF A GENERIC DRUG CONTAINS THE SAME ACTIVE INGREDIENT, IN THE SAME PHARMACEUTICAL FORM, AND IN THE SAME LEVEL OF CONCENTRATION AS THE ORIGINAL PRODUCT.*

*THE EFFICACY AND SAFETY PROFILES ARE DEPENDENT ON WHEN A DRUG BECOMES AVAILABLE FOR ACTIVITY IN THE TARGETED PART OF THE BODY: FOR EXAMPLE, THE TIME THAT IT WOULD TAKE FOR IT TO BE DISSOLVED — IF THE ACTIVE INGREDIENT MAKES CONTACT WITH A LIQUID MEDIUM — OR DISINTEGRATED — IF A TABLET BREAKS DOWN INTO PARTICLES WHEN ENTERING THE BODY.*

*DISINTEGRATION AND DISSOLUTION ARE FACTORS THAT COULD NEGATIVELY ALTER THE CLINICAL EFFICACY AND SAFETY PROFILES RELATIVE TO INNOVATORS. THEREFORE THERE NEED TO BE RULES TO ENSURE THAT GENERIC DRUG MAKERS MAKE PRODUCTS EQUIVALENT TO THE INNOVATOR DRUG.*

*ON MAY 12 1993, THE WORLD HEALTH ASSEMBLY ADOPTED RESOLUTION WHA 416, WITH THE PURPOSE OF ENDING ANY CONFUSION CAUSED BY THE MARKETING OF GENERIC DRUGS. THE MAIN REASON WAS DEFINING THE USE OF NON-PROPRIETARY NAMES AND TRADE MARKS IN CONNECTION WITH GENERIC DRUGS. HOWEVER, THE RESOLUTION HAS ALSO BEEN USEFUL FOR STRESSING THE DIFFERENCES BETWEEN GENERIC AND INNOVATOR DRUGS AND THE NEED FOR EQUIVALENCY RULES.*

*ACCORDINGLY, THE WORLD HEALTH ORGANIZATION (WHO) ASKED ITS MEMBER STATES TO ENCOURAGE PHARMACEUTICAL MANUFACTURERS TO CREATE AND MARKET GENERIC DRUGS AFTER THE CORRESPONDING PATENT TERMS HAD EXPIRED. WHILE MOST MEMBER STATES HAVE HAD A POSITIVE REACTION TO WHO'S RECOMMENDATIONS, APPROACHES HAVE BEEN RATHER DIFFERENT. THE MAJORITY OF COUNTRIES IN THE DEVELOPED WORLD HAVE ADOPTED THE FORMULA GENERIC/BIO-EQUIVALENCY, WHETHER IT IS USED UNDER A PARTICULAR MARK OR NOT.*

*OTHER COUNTRIES HAVE TAKEN ALTERNATIVE, AND QUESTIONABLE, ROUTES, FOR EXAMPLE BY HAVING DIRECTLY OR INDIRECTLY FOSTERED A MARKET FOR PSEUDO-GENERICS OR SO-CALLED SIMILARS. COUNTRIES THAT FOLLOWED THIS LINE HAVE MOSTLY STRUGGLED WHEN DICTATING QUALITY CONTROL RULES APPLICABLE TO AN EVER-GROWING SIMILARS INDUSTRY THAT HAS GAINED IN POWER AND MARKET SHARE.*