Brazil

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OVERVIEW OF REGULATORY AFFAIRS

DIMED (Drug Department) is in charge of regulatory affairs in Brazil. This department is part of the Secretaria de Vigilancia Sanitaria (Sanitary Surveillance Secretary). DIMED is also in charge of approval of blood products and medical devices. Other departments are in charge of approval of food, cosmetics and housecleaning products. The Secretaria de Vigilancia Sanitaria reports to the Minister of Health.

A new law and decree came into effect in Brazil in January 1977. It established the rules for submission and approval of pharmaceutical products. DIMED/Secretaria de Vigilancia Sanitaria issue some specific norms for dossier submission to the health authorities for certain products such as controlled products, over-the-counter (OTC) products, etc.

The ruling law/decree adopts several definitions and regulated subjects such as trademarks, renewal, changes of registration (e.g., change of composition, shelf life, packages, how supplied, new indications and new dosage), certificate cancellation, exemption of registration, importing and packaging. The decree also contains general procedures related to manufacturing release, technical responsibility, labeling and promotion practices, packaging containers, quality assurance, inspection requirements infringements and penalties.

The approval (free sale certificate) is granted for a period of five years and must be renewed every five years. Any changes related to composition, quality assurance and packaging (including packaging insert) must be applied for and depend on previous and express authorization of DIMED. Such changes must be recorded in registration documents. Within a period of 90 days, DIMED is obliged

to grant the approval or request additional information from the company. The department is not able to comply with this rule, however, due to a lack of structure, mainly human resources.

In order to obtain approval for a new chemical entity (NCE), the following are required:

- Application form (trademark, origin, product similarity, how supplied, shelf life, packaging, prescription requirement and complete composition).
- Submission fee (around US $600).
- Manufacturer's Authorization Certificate, issued by Secretaria de Vigilancia Sanitaria.
- Free sale certificate from the country of origin.
- Clinical Report containing the summary of preclinical trials, pharmacological and pharmacokinetics studies and clinical trials, including bibliography and literature.
- Product Technical Report containing the following items:
  - General information: pharmaceutical form and how supplied; complete composition; mode of use and/or dosage; indications; complementary therapeutic indications; contraindications; side effects; adverse reactions; restrictions; precautions; warnings; shelf life and storage.
  - Pharmacodynamics: pharmacological properties and pharmacokinetics; dosage (maximum and minimum per day); and justification for indicated dosage.
  - Quality assurance: complete composition with all components specified by technical names according to Denominacoes Comuns Brasileiras (DCB) [Brazilian chemical names]; manufacturing process (summary); descriptive quality control report of active substances as well as stability report of active substances and finished product; specifications or requirements and tolerance range for the tests; code or convention for batch number; report containing technical indications that there is neither physical nor chemical incompatibility between the package to be used and the product components; and handling and storage.
  - Complementary information: inscription in National Formulary or *Pharmacopeia*; bibliography about the product. DIMED may require reports if necessary for evaluation of scientific documentation, with a copy of its files; inclusion of narcotic, hypnotic or barbituric substances; and advantages of the product from a clinical point of view.
- Text of labels, package inserts and package.

- Manufacturer's Authorization Certificate issued by competent state authority.
- Declaration stating that the manufacturing facility (plant) has proper technical assistance from a legally capable pharmacist.
- Report containing indications, contraindications, side effects, adverse reactions, restrictions, precautions and warnings submitted for registration in the country of origin.
- Good Manufacturing Practice (GMP) procedures
- Manufacturer agreement with third parties, if applicable.

Note: All documents must be signed by the company's legal representative and by the pharmacist.

The above requirements for NCE registration are also applicable for products resulting from:

- change in concentration of active substance or in pharmacokinetic properties;
- active substance not registered for intended indication;
- active substance not registered as intended pharmaceutical form;
- withdrawal of active substance of an already registered product;
- substitution of active substance of an already registered product.
- new salt, despite the fact that the corresponding chemical entity has already been authorized by DIMED; and
- two or more active substances not registered together in a same product (combination).

For similar products, the requirements are the same as for NCE except for the Clinical Report. A product is considered to be similar if it contains the same therapeutic active substance(s), indications and dosage as other product currently registered in Brazil. When the similar product for which registration is being applied differs from the original by pharmaceutical form, dosage, or even indications, contraindications and side effects, it is essential to complement descriptive information with evidential scientific documentation, following new product registration procedures. DIMED may require updated scientific documents (registered or in the process of registration) at its convenience. The applicant shall indicate the similar product, mentioning its trademark and its registration number.

Companies may change several product characteristics such as composition (excipients), storage conditions, shelf life, packages, how supplied, manufacturing process, methods of quality control, package inserts, etc., and thus are required to submit the related documentation that supports the nature of change,

for instance, a) for a composition change (excipient, not active substance) the requests are new quality assurance, new stability reports and justification for the change; b) for a new indication the requests are clinical trials and dosage related to the new indication.

Certain products exempt from registration include those whose composition is duly recorded in the Brazilian *Pharmacopeia*, Codex or National Formulary accepted by Brazilian health authorities as well as formulas of easy manipulation in pharmacies or chemists.

The package insert must include: general information (DCB, pharmaceutical form (composition, how supplied); patient information (storage conditions, mode of use, main contraindications, adverse reactions, warnings, use in pregnancy, warning for the elderly); technical information (action/pharmaceutical properties and pharmacokinetics, indications, contraindications, adverse reactions, precautions, warnings, use in pregnancy, warning for the elderly, dosage, overdose); and legal information (type of product: under prescription or controlled product, psychotropic or OTC, registration number, manufacturer, address, pharmacist's name and inscription number).

In order to reach a general agreement for the Mercosur (Trade Agreement of the South Cone), the authorities may change some points of the law such as the new product concept, requirements for NCE approval, time to obtain approval and certain other points. However, the discussion is not yet finished and is moving at a slow pace.

The Sanitary Surveillance Agency was created in January 1999 and is currently being established. The main differences between it and the former agency, Secretaria de Vigilancia Sanitaria, are:

- higher registration fees (for instance, the submission fee for new drugs is currently set at US $50,000);
- new administrative structure; and
- no political influence over the Agency's affairs; its directors are nominated for three-year terms by the President of the Republic and are approved by the Senate.

In August 1999, Brazilian health authorities established a regulation for generic product registration.

ABOUT THE AUTHOR

Paulette Lopes graduated from the Pharmaceutical Sciences School of São Paulo University. She received a post-graduate degree in biochemistry from the Chemistry Institute of São Paulo University. Dr. Lopes worked as a regulatory affairs manager for Schering do Brasil and Novartis Biociencias before her current position at Akzo-Nobel in São Paulo.