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Skinny label in Brazil: drug authority seeking to implement new regulations

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The Brazilian healthcare legislation establishes in the legal definitions of generic drugs (article 3, items XX and XXI, Statute #6,360 of 1976[1]) that their labels must have all and the same therapeutic indications of the reference-listed drug. The law only allow differentiation in characteristics like product's size and shape, shelf life, package, and excipients[2].

The legislation at present doesn't allow any sort of skinny label or carve out. However, pressured by local generics companies, ANVISA (equivalent to the US FDA) recently issued a draft and "call for comments" of an amendment to its regulation. The new regulation would allow skinny label whenever there is a therapeutic indication protected by patent right.

ANVISA's current specific rule which establishes requirements for drugs' labels – Board of Directors' Rule #47 of 2009 – prohibits carve out. Article 14 of Rule #47 of 2009 sets that generics' labels must be in line with the structure and content of the reference-listed drug's label (which is considered the "standard label"[3]). ANVISA's regulation is even more clear on the prohibition of skinny labeling when it establishes exactly which pieces of information of generics' labels can differ from their standard label[4]. Therapeutic indications are not in this list.

In addition, ANVISA's regulation on post-approval changes for small molecules (Rule #73 of 2016) also reinforces the unlawfulness of skinny labeling in Brazil. It provides that only MA holders of drugs approved through the NDA pathway (which, as a rule, are the reference-listed ones) are allowed to request approval for including new therapeutic indications (Annex I, Item 11). Once the request is approved, MA holders of generics and branded generics must update their labels within the term of one hundred and eighty days[5]. There is no provision allowing requests for excluding an indication from generics and branded generics labels when it does not result from a previous change in the reference-listed drug's label.

On some occasions, ANVISA confirmed its understanding that skinny labeling is not allowed in Brazil, since *"generics and branded generics labels must contain exactly the same indications described in the reference-listed drug's one*"[6][7].

Notwithstanding, the Agency affirmed that there were *"internal discussions on the subject* [skinny label] *which have been raised after the BRPTO's decision to grant second medical use patents, but such discussions will only imply a change of position if they result in the amendment of Rule #47 of 2009*"***[8]***.

Some generic companies are updating ANVISA's public database with labels omitting patented uses[9]. Since this update occurs regardless of the Agency's analysis, it makes skinny labeling easier for approved drugs. ANVISA recognises that the lack of a previous examination allows such situation to happen[10].

But there are also cases in which ANVISA have granted the MAs for copies whose labels omitted patented uses[11]. And the label draft is one of the documents that have to be submitted within the application and that is analyzed prior to the granting. In this scenario, what can be called "non-statutory skinny labeling" is being implemented, violating the Brazilian legal framework, as well as ANVISA's official understanding.

In view of the pressure of local stakeholders, ANVISA has taken the first official step to change its understanding. On December 28, the Agency's Board of Directors published a "call for comments" (which will last 60 days, ending in March 2023) on the amendment of Rule #47 of 2009 to include an exemption allowing generics and branded generics to omit patented uses in their labels.

ANVISA has recognised that its current regulation must be changed in order to allow skinny labels to be authorized in Brazil. However, ANVISA has apparently not considered (at least until now) that it may also be necessary for Congress to amend the Brazilian Food & Drug Act. Naturally, if no changes to the Brazilian Food & Drug Act are made there will be room to question the legality of ANVISA's amendment to Rule #47 of 2009. Both steps need to be taken for certainty.

It is known that ANVISA has discussed with the Brazilian Association of Generic and Biosimilar Drugs (called "PróGenéricos") the possibility of legitimizing the practice even without any amendment. This would occur on the grounds of the sole paragraph of article 20 of Rule #47 of 2009[12], which certainly was not created for this situation. This provision is for the cases in which the MA holder of the reference-listed drug gets approval for a post-grant request that may not be applicable to the copy due to technical aspects of it. For instance, the provision would be potentially applicable if a new indication approved for the reference-listed drug was related to a specific strength for which the generic has not been approved. Besides not having this purpose, using such provision to allow skinny labeling violates the legal definitions of generic and branded generics.

Regardless, Brazilian generic-based companies should keep in mind that the lack of the patented indication in the product's label does not mean that the company is safe from patent infringement. Courts could review companies' behavior that could be considered inducement to the marketing of its product for the protected indication, despite not being mentioned on the product's label. Thus, skinny labeling should not be seen as a safe-harbor from patent infringement.

European and American Courts have been endorsing the understanding that, on a case-by case basis, it is necessary a holistic analysis of the company's behavior. As an example, it can be a sign of infringement if the marketing strategy induces doctors to prescribe the generic for the omitted therapeutic indication (GlaxoSmithKline v. Teva[13]).

Another relevant aspect to be checked is whether other parts of the label, such as the ones describing dosage and administration and adverse events, mentions the patented use (Amarin v. Hikma[14]). It was also found relevant the fact that the Defendant participated in a bid for the purchase of a drug but failed to inform the health insurance company that its product could not be used for the patented use (Novartis v. Sun[15]). Thinking about the Brazilian market reality, it is

especially important to analyze this behavior in sales within the Brazilian Public Healthcare System (which is called “SUS” in the Portuguese acronym). This is because, even if the drug is listed within formularies for more than one indication, as a rule, no distinction is made regarding the quantity for each intended use.

In summary, even if ANVISA changes its current rules to allow for skinny labels in Brazil, it should not be considered sufficient to conclude that there is no patent infringement. It is necessary to analyze the circumstances on a case-by-case basis, considering the entire marketing strategy adopted by the MA holders of generics and branded generics.

The fact that ANVISA is ignoring patent law when discussing a new rule, could create additional legal uncertainty to generic companies, generating more litigation in this regard.

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[1] Article 3rd. “Item XX – Branded Generic – Drug that contains the same APIs, strength, dosage form, route of administration, dosage and administration and therapeutic indications, and which is therapeutically equivalent to the drug approved by the competent authority, and that may differ only in characteristics related to the size and shape of the product, expiration date, packaging, labeling, excipients and vehicles, proven its effectiveness, safety and quality, and must always be identified by trade name or brand; Item XXI – Generic – Drug that is similar to the reference-listed one or to the innovator, and that is intended to be interchangeable with it, generally manufactured after the expiration or waiver of patent protection or other exclusivity rights, proven its effectiveness, safety and quality, and which is designated by the INN;”.

[2] Article 3rd. “Item XXII – Reference-listed drug – Innovator drug approved by the competent authority and marketed in the country, whose efficacy, safety and quality have been scientifically proven;”.

[3] Article 14. “Labels of generics and branded generics must be harmonized (form and content) with their respective Standard Label with respect to information on the efficacy and safety for the drug’s use.”

[4] Such as: (i) drug’s identification data; (ii) specific warnings, storage precautions, shelf life, preparation instructions, and occasional specific adverse reactions[4]; and (iii) MA number, MA holder and manufacturer’s identification data (article 14, paragraph 1st, Rule #47 of 2009).

[5] Rule #47 of 2009. “Article 20. Changes in labels of drugs that have Standard Labels, which are resulted from changes in their respective Standard Label, except for product-specific information, shall be notified electronically to Anvisa within ninety (90) days and made available within one hundred and eighty (180) days after publication of the Standard Label in the database, and shall be implemented, regardless of Anvisa’s prior analysis.”

[6] Statement received as a response of the FOIA request #25072.037692/2021-61.

[7] It should be highlighted that this prohibition is applicable only to small molecules. For biosimilars, the regulation established that the MA applicant shall indicate for which therapeutic indications it is seeking approval, which may differ from the originator product’s indications.

[8] Statement received as a response of the FOIA request #25072.027628/2022-53.

[9] Imatinib mesylate-based generic drug (Eurofarma Laboratórios S.A.); everolimus-based generic and branded generic drugs (Natcofarma do Brasil Ltda.).

[10] Statement received as a response of the FOIA requests #25072.026931/2021-58 and #25072.037692/2021-61.

[11] Lenalidomide-based generic and branded generic drugs (Eurofarma Laboratórios S.A.).

[12] Rule #47 of 2009. “Article 20. Changes in labels of drugs that have Standard Package Leaflets, linked to changes in their respective Standard Package Leaflets, except for product-specific information, the package leaflets shall be notified electronically within ninety (90) days and made available within one hundred and eighty (180) days after publication of the Standard Package Leaflets in the Electronic Bulletin, and shall be implemented, regardless of Anvisa’s prior analysis. Sole paragraph. Companies must evaluate whether changes related to posology, expansion of use, inclusion of a new route of administration and/or new therapeutic indication are applicable to their product. If not, there is no obligation to meet the deadline in the caput and the deadline will be evaluated case by case by Anvisa, depending on the post-registration change(s) that will be necessary for the adequacy of the product.”

[13] Available at: link.

[14] Available at: link.

[15] Available at: link.

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