GLP 5 Batch Analysis - A Step-wise Process for Brazil Registration

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Usted puede encontrar la versión en español de este artículo aquí. 'Análisis GLP de 5 lotes – Un proceso progresivo para registros en Brasila**'**

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Since the creation of synthetic pesticides during World War II, they are, today, extensively used for crop protection, food preservation, material preservation and disease control. These broadly fall into categories, such as fertilizers, herbicide, insecticides, and fungicides, are used in agriculture to assist in plant growth and protection. In order to market them, pesticides need to be registered, whether new or generic in the country where they are to be sold.

For the registration of a technical product, various tests, such as the 5-Batch analysis (for each active ingredient), information and characterization of impurities ≥ 0.1 % or other impurities of toxicological relevance, testing of physicochemical properties, ecotoxicology studies, acute and chronic toxicology studies are mandatory. A dossier, including these tests results, is submitted to the relevant regulatory body. The information also includes detailed discussions on manufacturing processes, impurity formation side reactions with emphasis on process impurities (organic, inorganic and residual solvents), starting materials and degradation products.

The 5-Batch analyses test qualifies the manufacturers products to reference specifications, as per respective guidelines, to ensure quality and safety of the product. For Brazilian requirements, five sequential batches from the final manufacturing process are selected. Detailed information on the manufacturing process, starting materials, intermediates, side reactions, byproducts, solvents, inorganic salts and catalysts and more, are collected. It is also necessary to predict the possible pathways of impurity formations, followed by the screening of samples for all probable organic and inorganic impurities. Additionally, a 3-D chromatogram is also obtained, as evidence of separation of all related components on a HPLC-PDA detector. A detailed method validation is done, followed by a 5-Batch analysis.

The entire analysis is done in 3 phases:

a) The preliminary phase, which includes qualitative information of all components in the product, a 2 D chromatogram to show that all components and related impurities have been separated, using either HPLC or GC, on columns of varying polarities and at various wavelengths, and a 3 D chromatogram.
b) Method validation, as per SANCO 3030/99 Rev 5 and OPPTS 830.1800
c) 5-Batch testing, as per SANCO 3030/99 Rev 5 and OPPTS 830.1700

A chromatographic method, such as gas chromatograph (GC) coupled with FID/MS/NPD/ECD system or liquid chromatograph (LC) coupled with PDA/UV/MS/ELSD system and/or ICP-OES /MS, are developed, which separates all related impurities and

active ingredients or inorganic impurities. The chromatography is performed on columns of varying polarities, in combination with varying polarities of the mobile phase. In order to ensure that there are no retained or co-eluting impurities, the mobile phase organic and aqueous phase are programmed to run from 100% aqueous to 100% organic. Volatile impurities or residual solvents are determined by Gas chromatography. Inorganic salts, or elemental impurities are determined by Ion Chromatography and ICP-OES/MS, respectively.

Any unknown impurity or degradation product ≥ 0.1 % needs to be further investigated. Also, impurities that are proven to be highly toxic need to be investigated and limited. Investigation/characterization may include impurity enrichment, isolation, separation synthesis and/or structure elucidation, using a series of hyphenated techniques, such as FT-IR, FT-Raman, LC, LC-MS, HRMS, GC/MS, NMR, LC-NMR, Multidimensional NMR, or others.

All these tests and determinations are common across all regulatory bodies, including,

- Europe: Regulation (EC) 1107/2009, Commission Regulation (EU) No 283/2013 and Annex
  (Section 5) of Regulation (EU) No 284/2013, SANCO 3030/99 rev.5, 22 March 2019.
- US-EPA: OPPTS 830.1550, OPPTS 830.1700, OPPTS 830.1800
- Brazil: ABNT NBR 14029: 2005, NBR 14029-2016.
- Worldwide: FAO or IUPAC specifications on toxicological relevant impurities

The 3D Chromatogram of impurities, separated on LC-UV-PDA, is submitted along with other test data. This highlights information on additional impurities, if any. This is a feature of HPLC using a photodiode array detector. A conventional 2D chromatogram has time as the x-axis and the detector signal as the y-axis. The third dimension of wavelength is included to check for any co-eluting impurity or any other unexpected impurity, contaminant, degradation product, etc., which might have an absorption maximum at a wavelength, other than the experimental wavelength. Various views of the 3D chromatogram are included to avoid any possibility of skipping an impurity peak. The 3D picture helps identify any impurity exhibiting a UV absorbance at a wavelength other than that selected in the 2D chromatogram. The overlaid spectrum shows that the peaks are pure and there is no peak hiding behind the impurity or the main peak. This helps sponsors and regulators to have a clear idea, at a glance, on additional impurities which may have been, knowingly or unknowingly, hiding in the chromatogram.

Thus, this 3 D data helps to identify the peak of a compound, if "pure" or not. This concept of peak purity is very relevant, in terms of identifying the presence or absence of peaks of other compound(s). This helps the sponsor, in terms of understanding and modifying the process/es to ensure that it is under control, and also to the regulator to look at safe and efficacious compounds of desired quality and strength.

At JRF, the 5-Batch analysis team is experienced in performing these set of tests and we have a strong legacy of successful regulatory submissions for more than 25 years. We also offer regulatory guidance to our sponsors for their product registrations in competitive timelines. Our expertise is reflected in the quality of our reports and dossiers, which are accepted by regulatory bodies around the globe. Our team is comprised of experts in chemistry, with masters and doctoral degrees, more than 50+ study directors and over 110+ study personnel. JRF has a state-of-the art GLP compliant laboratory to run 5-Batch analyses and other studies, with latest instruments, including LC-UV/PDA, LC-MS/MS, ICP-OES/MS, GC-FID/NPD/FPD/MS, and others.

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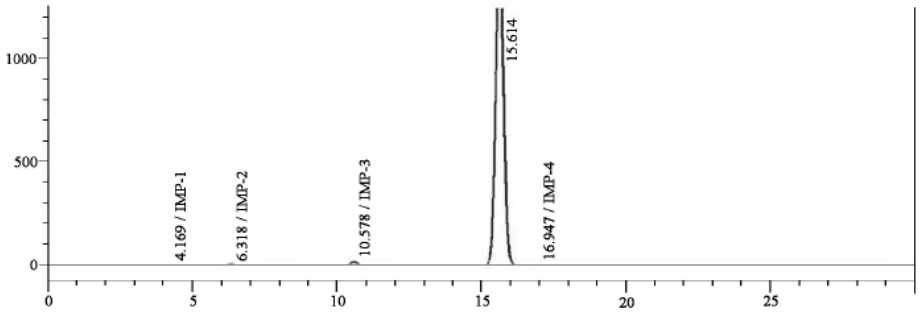

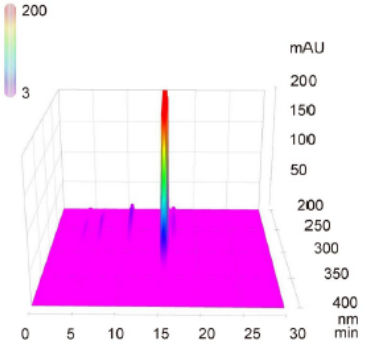

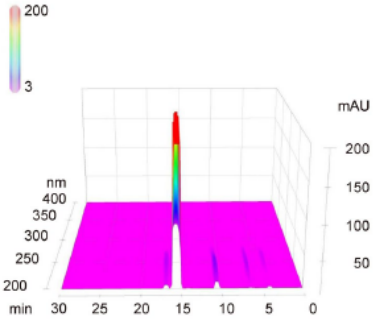

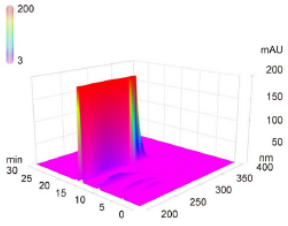

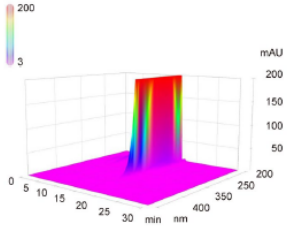

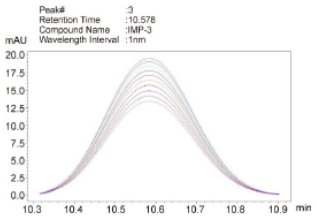

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