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Establishing the document required to prove Good Manufacturing Practices for Active Pharmaceutical Ingredients (API), when filing for the registration or post-registration of medicines, in compliance with RDC 753/2022 and RDC 73/2016.

1. Report

This document presents the understanding of the Synthetic Medicines Quality Assessment Management (GQMED), the Coordination for the Registration of Active Pharmaceutical Ingredients (Coifa) and the Coordination of Inspection and Sanitary Supervision of Pharmaceutical Ingredients (Coins) regarding the document required to prove Good Manufacturing Practices for Active Pharmaceutical Ingredients (API), when filing for registration or post- registration of medicines, in compliance with RDC 753/2022 and RDC 73/2016.

Considering the frequent questions regarding the need to apply for a Certificate of Good Manufacturing Practice (CBPF) for API manufacturing sites, the aim of this document is to provide clarity regarding the regulatory requirements, ensuring that everyone involved understands the guidelines and expectations of the technical areas involved.

2. Analysis

In the context of the registration and post-registration of synthetic and semi-synthetic medicines, for the purposes of the applicability of RDC 753/2022, RDC 73/2016 and RDC 359/2020, API manufacturers are considered to be all those responsible for the manufacturing stages of intermediates and APIs, for quality control of the API, from the introduction of the starting material(s), including the units responsible for physical

stages (milling, micronization, lyophilization) and sterilization, when these stages are carried out under the responsibility of the holder of the Active Pharmaceutical Ingredient Dossier (DIFA), as well as contracted companies.

The manufacture of the API comprises all the operations that include the acquisition of materials, production, quality control, release, storage, dispatch of finished products and the related controls, in accordance with article 6, item XXVI of RDC 654/2022.

Production, in turn, includes all the operations involved in preparing the active pharmaceutical ingredient, from receiving the materials to processing and packaging, according to art. 6, item LVI of RDC 654/2022.

The manufacture of APIs, from the introduction of the starting material, can involve the participation of more than one manufacturing site in the synthesis of the API, physical processing and packaging.

Compliance with good manufacturing practices is mandatory for all sites involved in the manufacture of the API from the introduction of the starting material, under the terms of RDC 654/2022.

It can be seen that the need for strict compliance with Good Manufacturing Practices for APIs becomes even more critical as the process progresses to the final stages of synthesis, purification and packaging, as highlighted in Table 1 of the ICH Q7 Guide.

Regarding the requirement of CBPF for APIs at the time of the drug registration or post-registration protocol, RDC 753/2022, which provides for drug registration, in its article 16, establishes the following requirements for APIs:

> *"Art. 16: When filing an application for registration of a drug product, the applicant for registration must submit the following information regarding the API:*
> *(...)*
> *II - a declaration signed by the technical manager or a person designated by him certifying that the manufacture of the API is conducted in accordance with Good Manufacturing Practice for APIs, starting with the introduction of the starting materials;*
> *III - file number of the API CBPF application, in accordance with the Collegiate Board Resolution (RDC) on the certification of good manufacturing practices for APIs;*
> *(...)*
> *§ Paragraph 2. The granting of drug product registration is conditional on the valid CBPF and CADIFA for the API. (...)*

§ Paragraph 5 For the purposes of item II of the main body of this article, the declaration must be based on an audit of Good Manufacturing Practices conducted under the terms of the Resolution of the Collegiate Board of Directors (RDC) that sets out the general guidelines for good manufacturing practices for drug products."

RDC 73/2016, which deals with the post-registration of medicines, also requires the submission of the file number of the API CBPF application, in accordance with the Resolution of the Collegiate Board of Directors - RDC that deals with the certification of good manufacturing practices for APIs, for changes "1a", "1d", "1e", "1f", "1g", "1h", "1j", "1k", "1l", "10a" and "10b".

It should be noted that for changes "1d", "1e", "1j" and "1k", the document only applies to the change associated with a new manufacturing site; and for changes "10a" and "10b" only when they are associated with a request for a Letter of Adequacy for Active Pharmaceutical Ingredients Dossier (CADIFA).

It is important to note that CADIFA, when associated with a drug registration, is linked in its entirety, comprising all the sites described in CADIFA. Therefore, it is not possible to use only some of the manufacturers listed in CADIFA.

Furthermore, for all cases, the granting of registration and post-registration of the drug is conditional on the valid CADIFA and CBPF for the API.

Thus, considering the various manufacturers involved in the manufacture of the API, from the introduction of the starting material(s), it is essential to adopt a pragmatic and risk-based approach to establishing the document required to prove Good Manufacturing Practices, as provided for in RDC 753/2022 and RDC 73/2016.

In this scenario, the following table exemplifies the sites involved in manufacturing process of the API and the document required to prove Good Manufacturing Practices:

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API manufacturing steps	CBPF issued by Anvisa[1]	*CBPF or document issued by the health authority of the country where the production establishment is located attesting to satisfactory compliance with good manufacturing practices*[2]	Declaration signed by the technical manager or their designee attesting that the manufacture of the API is conducted in accordance with Good Manufacturing Practices for APIs, starting with the introduction of the starting materials[3]
Complete API synthesis (from the starting material)	X	-	X
Last stage of chemical transformation of API[4]	X	-	X
Final stage of isolation and purification of API[5]	X	-	X
Synthesis of the intermediate that is also classified as an API. Example: Venlafaxine, which can be marketed as a final API or as an intermediate.	X	-	X
Synthesis of API obtained directly by fermentation	X	-	X
Synthesis from the starting material to the step prior to the last chemical transformation of the API[4]	-	X	X
Physical steps and sterilization[6]	-	X	X

[1] For the purposes of registration and post-registration, the company must provide the file number of the CBPF application for the API at the time of filing, in accordance with the Collegiate Board Resolution (RDC) on the certification of good manufacturing practices for APIs. Approval of the petition is conditional on a valid CBPF.

[2] In addition, a declaration must be submitted by the API manufacturer attesting that there is no divergence in the manufacture and controls adopted for the API that will be supplied for the manufacture of the drug products destined for the Brazilian market.

[3] The declaration must be issued by the applicant for registration or post-registration of the drug product and must be based on an audit of good manufacturing practices conducted under the terms of the Resolution of the Collegiate Board of Directors - RDC, which sets out the general guidelines for good manufacturing practices for drugs products.

[4] Step involved in synthesizing the chemical structure of the API from precursor molecular fragments. It usually involves C-X or C-C bond formation or breaking (item 11. Glossary, ICH Guide Q11). In this context, chemical transformation steps such as salification, neutralization, enantiomeric resolution, crystallization, purification, mixing, milling and micronization are not considered.

[5] They include the salification, neutralization and chiral resolution steps.

[6] It also applies to the physical steps and sterilization that are the responsibility of the drug product holder.

Therefore, it is recommended that, during the Good Manufacturing Practices audit stage, conducted under the terms of the RDC that provides for general guidelines on good manufacturing practices for drug products, the manufacturer of the drug product assesses with the DIFA holder the locations where the critical stages of the API manufacturing process are carried out, so , at the time of filing the application for registration or post- registration, all establishments involved in the manufacture of the API from the introduction of the starting material comply with Good Manufacturing Practices under the terms of RDC 672/2022 and this Technical Note.

3. Conclusion

Considering the various manufacturers involved in API manufacturing process, from the introduction of the starting material(s), it is essential to adopt a pragmatic and risk-based approach to establish the document necessary to prove Good Manufacturing Practices, as provided for in RDC 753/2022 and RDC 73/2016.

It should be noted that the cases exemplified in this Technical Note are intended to provide transparency and predictability as to the Agency's expectations for proof of Good Manufacturing Practices for APIs when filing for registration or post-registration of drug products, in compliance with RDC 753/2022 and RDC 73/2016. However, this understanding does not limit the applicability of art. 5, § 2, of RDC 672/2022, which provides that Anvisa may, upon request, require CBPF for API intermediates.

In addition, it should be emphasized that all international establishments involved in the manufacture of API used in drug products in Brazil, regardless of the request for CBPF by Anvisa in a drug registration or post-registration rule, may have a routine or investigative health inspection by Anvisa, as part of the Inspection Program, under the terms of RDC 672/2022.