COLLEGIATE BOARD RESOLUTION – RDC NO. 73 OF 7 APRIL 2016.

(Published on the Federal Official Gazette no. 67 of 8 April 2016)

(Rectified on the Federal Official Gazette no. 68 of 11 April 2016, because its title was published as Brazilian Supplementary Health Agency, instead of Brazilian Health Regulatory Agency)

Provides for post-marketing authorization alterations, cancellation of marketing authorization for medicinal products with synthetic and semisynthetic active ingredients, and gives other provisions.

The Collegiate Board of Directors of the Brazilian Health Regulatory Agency, in the use of the attributions vested in it under Article 15, items III and IV, and Article 7, items III and IV of Law no. 9,782 of 26 January 1999, and item V, paragraphs 1 and 3 of Article 53 of the Internal Regulation approved in the terms of Annex I of Collegiate Board Resolution – RDC no. 61 of 3 February 2016, adopts the following Collegiate Board Resolution, as decided upon in a meeting held on 22 March 2016, and I, Director-President, determine its publication.

Article 1. The Technical Regulation that establishes the procedures for post-marketing authorization alterations and cancellation of marketing authorization of medicinal products is approved in accordance with the terms of this Resolution.

CHAPTER I

INITIAL PROVISIONS

Section I

Objective

Article 2. This Resolution has the objective to classify post-marketing authorization alterations in medicinal products, establish the criteria and the minimum necessary documentation, provide for direct responsibilities of companies and establish the simplified procedure for post-marketing authorization alterations requiring immediate implementation in accordance with the classification of the alteration established in this Resolution, in order to ensure the quality, safety, and efficacy of these medicinal products.

Section II

Scope

Article 3. This Resolution applies to all medicinal products with synthetic and semisynthetic active ingredients classified as new, similar, and generic.

Section III

Definitions

Article 4. For the purposes of this Resolution, the following definitions are adopted:

I – Product Alteration History (PAH): document available in the company, in which information regarding the annual product history must be recorded;

II – Stability study protocol: document that defines the stability study plan, including tests and acceptance criteria, schedule, characteristics of the batch to be submitted to the study, quantity of samples, study conditions, analytical methods, and packaging materials;

III – Multiple concomitant alterations: alterations resulting from a main alteration provided for in this Resolution;

IV – Multiple parallel alterations: two or more directly related, simultaneous alterations, submitted jointly;

V – Ordinary procedure: petition procedure that requires submission and must await for a favorable manifestation from Anvisa for implementation;

VI – Simplified procedure: simplification of the petitioning ordinary procedure, exclusively for the petitions classified as immediate implementation by this regulation;

VII – Company´s Technical Analysis Opinion (CTAO): opinion developed by the marketing authorization holding company, which covers at least all criteria and documents provided for in this Resolution and related health regulations, including a critical assessment of all relevant aspects for Anvisa´s analysis. The CTAO must ensure that the criteria and documents presented to the health authority aiming at the maintenance of quality, safety, and efficacy parameters of the product were met and approved;

VIII – Suspension of simplified procedure: condition in which the company is unable to perform the simplified procedure for a certain period; and

IX – Alteration of immediate implementation: post-marketing authorization alteration to which Anvisa grants prior approval for its immediate implementation by the company, through the inclusion in the PAH, or in the petition submitted individually, of all the satisfactory evidences required for the alteration, as provided for in this regulation.

CHAPTER II

PROVISIONS ABOUT CLASSIFICATION AND SUBMISSION OF POST-MARKETING AUTHORIZATION ALTERATIONS

Article 5. Post-marketing authorization alterations are classified according to their potential impact on the quality, safety, and efficacy of the medicinal product, which may be of immediate implementation, with or without individual submission, or depend on Anvisa’s prior approval.

Paragraph 1. The alterations classified as of immediate implementation according to this Resolution, whose company identifies a potential significant impact on quality, safety, and efficacy of the medicinal product, must be petitioned in accordance with the ordinary procedure, with relevant subject, and shall await for Anvisa's manifestation for its implementation.

Paragraph 2. The company suspended from submitting following the simplified procedure, in accordance with Articles 36 and 45, must submit according to the ordinary procedure all post-marketing authorization alterations of its ownership.

Article 6. Immediate implementation alterations shall be allowed when all required evidences are attached to the PAH available at the company or to the individual petition submitted, except when such alteration is parallel to another requiring prior approval, when the implementation of the alterations and the PAH filling must be carried out only after Anvisa's approval.

Paragraph 1. The immediate implementation of the alterations does not hinder the analysis, at any time, of the required documentation, and may be ratified or rejected.

Paragraph 2. In case of rejection, the conditions prior to the alteration must be re-established immediately after Anvisa's manifestation or the medicinal product manufacturing must be temporarily discontinued.

Article 7. Alterations requiring prior approval must be submitted and await for Anvisa's analysis and favorable manifestation in order to be implemented.

Paragraph 1. After approval, the company will have up to 180 (one hundred and eighty) days to implement the alteration, except when there is contrary manifestation from Anvisa.

Paragraph 2. After production of the first batch with the approved alteration, the production of batches in a different condition shall not be allowed.

Article 8. When there is more than one simultaneous alteration to the same presentation, concentration, and pharmaceutical form, the company shall be able to submit such alterations in parallel or concomitantly.

Article 9. In cases of parallel alterations, the company must submit each individual alteration presenting unique documentation covering all evidences relating to each subject of the petition.

Paragraph 1. The description of parallel alterations and their correlation must be included in the justification referred to in article 15, item III, of this Resolution.

Paragraph 2. The petitioner must present the assessment of the additive effect of individual parallel alterations with regard to the potential impact on quality, safety, and efficacy of the medicinal product and present additional evidences, when necessary.

Article 10. In cases of concomitant alterations, the petition must refer to the main alteration and the information about the concomitant alteration must be described in the justification.

Paragraph 1. The only alterations that shall be considered as concomitant are those explicit in this Resolution.

Paragraph 2. The evidences related to all alterations must be presented.

Paragraph 3. When the documentation requested for concomitant alterations is divergent, the documentation related to the main alteration must be presented.

Article 11. In cases of post-marketing authorization alterations not provided for in this Resolution, the company must contact Anvisa to establish the tests and the documentation that must be presented.

Article 12. Post-marketing authorization alterations provided for in this Resolution are described in Annex I of this regulation.

~~Paragraph 1. The alterations related to the active pharmaceutical ingredient are described in Annex I, item 1 (one), modifications a; b; c; d; e.~~

Paragraph 1. Alterations related to the active pharmaceutical ingredient (API) are described in Annex I, item 1 (one), alterations a; b; c; d; e; f; g; h; i; j; k; l. **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

Paragraph 1-A. For the replacement or inclusion of a new Active Pharmaceutical Ingredient Dossier (DIFA) without the Active Pharmaceutical Ingredient Dossier Adequacy Letter (CADIFA), the medicinal product marketing authorization holder must file alteration "1a". **(Included by Resolution – RDC no. 361 of 27 March 2020)**

Paragraph 1-B. For API without CADIFA, the medicinal product marketing authorization holder must file all alterations related to the API provided for in the Collegiate Board Resolution – RDC that establishes the DIFA and the CADIFA, through alterations "1b", "1c", "1d", "1e", and "1f". **(Included by Resolution – RDC no. 361 of 27 March 2020)**

Paragraph 1-C. For the inclusion or replacement of CADIFA holder, the medicinal product marketing authorization holder must file alteration "1g" or "1h". **(Included by Resolution – RDC no. 361 of 27 March 2020)**

Paragraph 1-D. For API with CADIFA, when the DIFA alteration implies revision of the CADIFA, the medicinal product marketing authorization holder must file the medicinal product post-marketing authorization alteration only after approval of the DIFA alteration or expiry of the period for implementation, through alterations "1i", "1j", and "1k". **(Included by Resolution – RDC no. 361 of 27 March 2020)**

Paragraph 1-E. For API with CADIFA, when the DIFA alteration does not imply revision of the CADIFA, the medicinal product marketing authorization holder must not file a post-marketing authorization alteration of the medicinal product. **(Included by Resolution – RDC no. 361 of 27 March 2020)**

Paragraph 1-F. For API with CADIFA, the medicinal product marketing authorization holder must also file the API alterations of stages of the manufacturing process that are not included in the DIFA (e.g. sterilization, physical steps), where applicable, through alterations "1b", "1c", "1d", and "1e". **(Included by Resolution – RDC no. 361 of 27 March 2020)**

~~Paragraph 2. The alterations related to tests, specification limits, and analytical methods of quality control and stability of the active pharmaceutical ingredient and medicinal product are described in Annex I, item 2 (two), modifications a; b; c; d; e; f; g; h.~~

Paragraph 2. Alterations related to tests, specification limits, and analytical methods of quality control and stability of the active pharmaceutical ingredient and medicinal product are described in Annex I, item 2 (two), alterations a; b; c; d; e; f; g. **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

Paragraph 3. The alterations related to tests, specifications limits, and excipient quality control methods are described in Annex I, item 3 (three), modification a.

Paragraph 4. The alterations related to medicinal product description and composition are described in Annex I, item 4 (four), modifications a; b; c; d; e; f; g; h; i; j; k; l; m; n.

Paragraph 5. The alterations related to the site of one or more steps of the medicinal product productive process are described in Annex I, item 5 (five), modifications a; b; c; d; e; f; g; h.

Paragraph 6. The alterations related to the production process of the medicinal product, equipment, and batch size are described in Annex I, item 6 (six), modifications a; b; c; d; e; f; g.

Paragraph 7. The alterations related to the medicinal product packaging are described in Annex I, item 7 (seven), modifications a; b; c; d; e; f; g; h; i; j; k; l.

Paragraph 8. The alteration related to inclusion of new presentation is described in Annex I, item 8 (eight), modification a.

Paragraph 9. The alterations related to the medicinal product shelf life or conservation care are described in Annex I, item 9 (nine), modifications a; b; c; d.

Paragraph 10. The inclusion of new concentration is described in Annex I, item 10 (ten), modifications a; b.

Paragraph 11. The alterations related to dosage, use expansion, inclusion of new administration route and new therapeutic indication are described in Annex I, item 11 (eleven), modifications a; b; c; d.

Paragraph 12. The alterations related to the medicinal product name, medicinal product marketing authorization cancellation and exclusion of active pharmaceutical ingredient manufacturing site, primary packaging site, secondary packaging site, and/ or product manufacturing site are described in Annex I, item 12 (twelve), modifications a; b; c; d.

CHAPTER III

GENERAL PROVISIONS REFERRING TO DOCUMENTATION

Article 13. The documentation requested for each modification is described in Annex I of this Resolution.

Sole paragraph. When any of the required documents is not applicable, the lack of presentation of it must be accompanied by technical justification and data to support its absence.

Article 14. All documentation must be in accordance with the specific legislation in force and, if there is a guide, it must be consulted and adopted as applicable.

Paragraph 1. Specific rules, such as those that establish the criteria for biowaiver, analytical methodology validation, and stability study may serve as a basis for the absence of documentation required in this Resolution.

Paragraph 2. In the absence of specific legislation and guides, the company must discuss with Anvisa, prior to the petition submission, the presentation of additional evidences.

Article 15. All petitions of post-marketing authorization alterations and medicinal product marketing authorization cancellation must be accompanied by the following documents:

I – Federal Collection Slip (GRU, in Portuguese) related to the Health Surveillance Inspection Fee (TFVS, in Portuguese) accompanied by the respective payment proof or exempt GRU, where applicable;

II – Petition forms duly filled;

III – Request justification, including the detailed description and the proposal rational, in accordance with Annex II; and

IV – Company´s Technical Analysis Opinion (CTAO).

Paragraph 1. The Product Alteration History petition waives the presentation of Petition Forms.

Paragraph 2. The petitions of medicinal product marketing authorization cancellation and of the presentation waive the CTAO presentation.

Paragraph 3. The petitioner of post-marketing authorization alteration must present the CTAO in hard copy and in media, in order to allow textual search and copy.

Paragraph 4. The CTAO must be signed by the technical responsible officer, the quality assurance responsible officer, the officer responsible for regulatory affairs at the marketing authorization holder, and by other officers responsible for the alteration. Further guidance regarding the CTAO shall be made available at Anvisa's website.

Article 16. The stability study data generated after the presentation of the stability protocol or of the incomplete stability study, related to the immediate implementation petitions and to the approved petitions, must be included in the Product Alteration History, even if the study is not concluded.

Article 17. In cases where the process validation protocol is required, the validation summary report generated subsequently must be included in the Product Alteration History.

Article 18. Out-of-specification results of the stability study in progress must be reported immediately to Anvisa after preliminary investigation, including the assessment of the need to apply a precautionary measure.

Sole paragraph. The corrective action proposal must be sent subsequently to the investigation conclusion.

Article 19. The medicinal product shelf life shall be defined in accordance with the stability results presented.

Paragraph 1. For petitions that must await for Anvisa's favorable manifestation, in which the stability study submitted confirms a temporary shelf life shorter than the one authorized, this shall be reduced and the petitioning for shelf life reduction shall not be necessary.

Paragraph 2. For immediate implementation petitions, in which the stability study submitted confirms a temporary shelf life shorter than the one authorized, the company must petition shelf life reduction.

Paragraph 3. In cases where stability study protocol is required, the shelf life authorized shall be maintained.

Article 20. The forms contained in Annexes II and IV referred to in this Resolution must be presented in accordance with the proposed models.

Sole paragraph. Annex II form must be duly signed by the technical responsible officer, the quality assurance responsible officer, and the officer responsible for regulatory affairs at the marketing authorization holder.

Article 21. It shall not be necessary to attach to the petition the new package insert leaflet and label text models for post-marketing authorization alterations that require update of such texts, except when requested in this Resolution or at Anvisa´s discretion.

Sole paragraph. The company must update the information on the package insert leaflet and label in accordance with the post-marketing authorization alterations.

Article 22. In cases where the post-marketing authorization alteration refers to more than one concentration of the same pharmaceutical form, this must be submitted with batch production order referring at least to the highest and the lowest concentration, provided that the formulations are qualitatively equal, proportional, and manufactured at the same site, with the same productive process.

Sole paragraph. In the cases referred to in the caption of this article, a justification based on a comparison of the characteristics of formulations and the productive process of the different concentrations must be presented.

Article 23. In cases where more than one medicinal product manufacturing site, more than one active ingredient manufacturing site, more than one productive process, or more than one packaging form are proposed, among other alterations, failure to submit the required evidences including all possible combinations between the conditions authorized and the alterations proposed must be technically based, with information and history that can justify its absence.

Article 24. When a post-marketing authorization alteration requires technical documents, such as production report, stability studies, quality control reports, among others, there shall be an assessment regarding the medicinal product manufacturer’s Good Manufacturing Practices conditions existing at the time of batch production, as well as reports and respective analyses that were submitted to Anvisa.

Sole paragraph. The assessment of the Good Manufacturing Practices conditions referred to in the caption of this article may result in validation or invalidation of the documents presented.

Article 25. For similar and generic medicinal products, in the post-marketing authorization alterations where a technical report of relative bioavailability/ bioequivalence study is requested, the study must be conducted between the medicinal product proposed and the reference medicinal product.

CHAPTER IV

PRODUCT ALTERATION HISTORY

Article 26. The marketing authorization holder is responsible for the PAH, and the company must fill in and attach the appropriate documentation for each process.

Article 27. All post-marketing authorization alterations must be recorded in the PAH simultaneously to the date of their implementation and/ or approval.

Article 28. When the alteration is of immediate implementation and does not require individual submission, the documentation required for each alteration established in Annex I of this Resolution, including the CTAO, must be attached to the PAH on date of the implementation referred to.

Article 29. The PAH must contain the following information:

I – all post-marketing authorization alterations of immediate implementation, with or without submission, as well as those that had prior approval by Anvisa;

II – additional information, including:

a) the list of batches manufactured or imported in the year, intended exclusively for commercialization in the Brazilian market, including manufacturing date, batch number and size (mass/ volume and pharmacotechnical units);

b) last version of the document(s) including tests, specification limits, and medicinal product quality control analytical methods, as approved;

c) completed follow up stability study reports and documents referred to in articles 16 and 17; and

d) other information not characterized as post-marketing authorization alterations, but considered as updates of the information presented in the marketing authorization.

Article 30. The PAH must be updated and easily available at the company for presentation to the health authority when required.

Article 31. The PAH data must be submitted annually, in the month of the anniversary of the medicinal product marketing authorization, even in the absence of post-marketing authorization alterations, and it must refer to the period of 12 (twelve) months prior to its submission.

Sole paragraph. PAH submission must be done through electronic petitioning and the electronic petition modality must selected, without the need to send the documentation in hard copies.

CHAPTER V

FINAL AND TRANSITIONAL PROVISIONS

Article 32. Anvisa´s decisions regarding the assessment of post-marketing authorization requests shall be published in the Federal Official Gazette, or in another mean of institutional publication, when applicable.

Article 33. Anvisa´s guidelines for post-marketing authorization alterations in medicinal products shall be made available for consultation on this Agency's website.

Article 34. The Company´s Technical Opinion (CTAO) may be published in accordance with the criteria to be established by the Anvisa, and the confidential information shall be protected.

~~Article 35. The post-marketing authorization petitions included in the scope of this regulation submitted before the date this Resolution enters into force, including those currently under~~

~~review at the General-Office of Medicinal Products, shall be analyzed in accordance with the Resolutions in force at the time of submission.~~

~~Paragraph 1. The petitions already submitted, the analysis of which has not yet started, and the object of which is classified by this regulation as of immediate implementation to be submitted in the PAH, may be implemented in accordance with the provisions in Article 6, provided that the petition submitted is requested to be withdrawn.~~

~~Paragraph 2. The petitions already submitted, the analysis of which has not yet started, the object of which is classified by this regulation as of immediate implementation, and which are not petitioned via PAH may be implemented in accordance with the provisions in Article 6, provided that the alteration is formalized through specific amendment to the document referring to the post-marketing authorization alteration, including the following documents:~~

~~I – identification of the petition object and reclassification in accordance with the terms of Annex I of this regulation.~~

~~II – complementary documentation required in this regulation.~~

Article 35. The post-marketing authorization petitions included in the scope of this regulation submitted before the date this Resolution enters into force, including those currently under review at the General-Office of Medicinal Products, shall be analyzed in accordance with the Resolutions in force at the time of submission. **(Wording given by Resolution – RDC no. 120 of 3 November 2016, revoked by Resolution – RDC no. 121 of 4 November 2016)**

Paragraph 1. The companies shall have the option to apply the regulations herein to the petitions submitted before this Resolution comes into force. **(Wording given by Resolution – RDC no. 120 of 3 November 2016, revoked by Resolution – RDC no. 121 of 4 November 2016)**

Paragraph 2. The petitions already submitted, the analysis of which has not been initiated, the object of which is classified by this regulation as of immediate implementation to be submitted in the PCH, may be implemented in accordance with the provisions in Article 6, provided that the petition submitted is requested to be waived. **(Wording given by Resolution – RDC no. 120 of 3 November 2016, revoked by Resolution – RDC no. 121 of 4 November 2016)**

Paragraph 3. The petitions already submitted, the analysis of which has not been initiated, the object of which is classified by this regulation as of immediate implementation, and which are no submitted via PCH, may be implemented in accordance with the provisions in Article 6, as long as there is formalization of the alteration carried out through specific addition to the documentation referring to the post-marketing authorization alteration, including the following documents: **(Wording given by Resolution – RDC no. 120 of 3 November 2016, revoked by Resolution – RDC no. 121 of 4 November 2016)**

I – Identification of the petition object and reclassification in the terms of Annex I of this Resolution. **(Wording given by Resolution – RDC no. 120 of 3 November 2016, revoked by Resolution – RDC no. 121 of 4 November 2016)**

II – Complementary documentation required in this Resolution. **(Wording given by Resolution – RDC no. 120 of 3 November 2016, revoked by Resolution – RDC no. 121 of 4 November 2016)**

Article 36. When irregularities are detected in the petitions of immediate implementation, the company may be suspended from conducting the simplified procedure for post-marketing authorization alterations.

Paragraph 1. The absence of required evidences or failed evidences for the alteration on the date of implementation, in accordance with Annex I of this Resolution, are considered irregularities.

Paragraph 2. The company suspended from conducting the simplified procedure is prevented for 1 (one) year, from the date the suspension decision is published, to implement post-marketing authorization alterations without prior authorization by Anvisa for any medicinal product of its ownership.

Article 37. When the marketing authorization renewal petition is in appeal phase, the simplified procedure shall not be applicable for post-marketing authorization petitions of the corresponding process.

~~Article 38. Collegiate Board Resolution – RDC no. 48 of 6 October 2009 and Normative Instruction no. 11 of 6 October 2009 are hereby revoked.~~

Article 38. Collegiate Board Resolution – RDC no. 48 of 6 October 2009 and Normative Instruction no. 11 of 6 October 2009 remain in force up to and no later than 31 January 2017. **(Wording given by Resolution – RDC no. 121 of 4 November 2016, revoked by Resolution – RDC no. 292 of 24 June 2019)**

Paragraph 1. The companies have the option to submit new petitions for post-marketing authorization alterations in the terms of Collegiate Board Resolution – RDC no. 48 of 6 October 2009 and Normative Instruction no. 11 of 6 October 2009, or Collegiate Board Resolution no. 73 of 7 April 2016. **(Wording given by Resolution – RDC no. 121 of 4 November 2016, revoked by Resolution – RDC no. 292 of 24 June 2019)**

Paragraph 2. The submission referred to in Paragraph 1 must include in the field “observations” on the cover page of all new petitions for post-marketing authorization alterations the following highlighted phrases, accordingly: **(Wording given by Resolution – RDC no. 121 of 4 November 2016, revoked by Resolution – RDC no. 292 of 24 June 2019)**

I – “PETITION SUBMITTED IN THE TERMS OF RDC NO. 48/2009.”; **(Wording given by Resolution – RDC no. 121 of 4 November 2016, revoked by Resolution – RDC no. 292 of 24 June 2019)**

II - “PETITION SUBMITTED IN THE TERMS OF IN NO. 11/2009.”; or **(Wording given by Resolution – RDC no. 121 of 4 November 2016, revoked by Resolution – RDC no. 292 of 24 June 2019)**

III - “PETITION SUBMITTED IN THE TERMS OF RDC NO. 73/2016.”. **(Wording given by Resolution – RDC no. 121 of 4 November 2016, revoked by Resolution – RDC no. 292 of 24 June 2019)**

Article 39. Items 3.1.2, 3.1.3, 3.2, and 3.4 of the Annex to Normative Instruction no. 2 of 30 March 2009, published in the Federal Official Gazette of 1 April 2009, shall take effect with the following wording:

"3.1.....

3.1.2. In the case of solids, the minimum amount of 100,000 pharmacotechnical units or 10% of the industrial batch, whichever is greater, must be considered. (new wording)

3.1.3. Batches of solids smaller than 100,000 pharmacotechnical units may be presented for the purposes of marketing authorization and post-marketing authorization, provided that its size corresponds to the industrial batch intended. (new wording)

3.2. For batch size alterations, the company must be in accordance with the specific regulation on post-marketing authorization alterations." (new wording)

3.4. For products whose concentration of active ingredient in relation to the formula is lower than 2% (two percent), pilot batches with quantities different from industrial batches shall not be allowed.

Article 40. Pilot batches shall be accepted for the purposes of marketing authorization and post-marketing authorization of solids between 50,000 and 100,000 pharmacotechnical units, as long as they have been manufactured prior to the date this Resolution comes into force and the petition of which is submitted up to 1 (one) year from the effective date of this Resolution.

Sole paragraph. Pilot batches whose concentration of active ingredient is lower than 2% (two percent) and higher than 0.99 milligrams per dosage unit in relation to the formula shall be accepted for the purposes of marketing authorization and post-marketing authorization of solids, provided that they have been manufactured prior to the date this Resolution comes into force and the petition of which is submitted up to 1 (one) year from the effective date of this Resolution.

Article 41. For products with approved marketing authorization with pilot batches of solids manufactured between 50,000 and 100,000 pharmacotechnical units, the immediate implementation of batch size increase in up to 10 (ten) times shall be allowed, by means of individual protocol with specific subject code, meeting the following conditions:

I – petitioning for products authorized before the effective date of this Resolution must occur within a maximum period of 2 (two) years from the effective date of this Resolution;

II – petitioning for products authorized after the effective date of this Resolution must occur within a maximum period of 2 (two) years from the marketing authorization grant, and may not exceed 5 (five) years from the effective date of this Resolution;

III – the petition must include the relative bioavailability/ bioequivalence study schedule and the documents provided for in modification f, item 6 (six), Annex I.

The relative bioavailability/ bioequivalence technical report must be presented within a maximum period of 2 (two) years after petitioning.

Sole paragraph. Failure to present the relative bioavailability/ bioequivalence study in accordance with the terms of Article 41 shall result in marketing authorization cancellation.

Article 42. Articles 19, 20, and 21 of RDC no. 47 of 8 September 2009, published in the Federal Official Gazette of 9 September 2009, republished on 19 January 2010, shall enter into force with the following wording:

"Article 19. The alterations in the information provided for in package insert leaflets of medicinal products that do not have Standard Package Insert Leaflet due to a post-marketing authorization alteration must be made available concomitantly to their implementation.

Sole paragraph. The new versions of package insert leaflets must be submitted through notification of alteration in package insert leaflet text via electronic petitioning in up to 30 days after approval, and it has to include the information in the last package insert leaflets published in the Electronic Package Insert Leaflet List, in addition to the information approved in this petition." (new wording)

"Article 20. For alterations in the texts of package insert leaflets of medicinal products that have Standard Package Insert Leaflet, linked to the alterations of their respective Standard Package Insert Leaflets, except for product-specific information, the package insert leaflets must be notified electronically in up to 90 (ninety) days and made available in up to 180 (one hundred and eighty) days after the publication of the Standard Package Insert Leaflets in the Electronic Package Insert Leaflet List, and must be implemented, regardless of prior manifestation by Anvisa.

Sole paragraph. Companies must evaluate if the alterations related to dosage, use expansion, inclusion of new administration route and/ or new therapeutic indication are applicable to their product. If not, compliance with the deadline provided for in the caption of this article is not mandatory, and the deadline shall be analyzed by Anvisa on a case by case basis, depending on the post-marketing authorization alteration(s) that will be needed for the product suitability." (new wording)

"Article 21. Alterations in the information provided for in the package insert leaflets of generic and similar medicinal products due to a post-marketing authorization alteration must be made available concomitantly to their implementation.

Sole paragraph. The new versions of package insert leaflets must be submitted through notification of alteration in package insert leaflet text via electronic petitioning in up to 30 days after approval, including the information accordingly." (new wording)

Article 43. Article 76 of RDC no. 71 of 22 December 2009, published in the Federal Official Gazette of 23 December 2009, shall enter into force with the following wording:

"Article 76. Alterations of the information provided on the labelling as a result of a post-marketing authorization alteration must be available concomitantly to their implementation.

Sole paragraph. The new labelling models must be submitted through labelling notification via electronic petitioning in up to 30 days after approval, containing the latest model of labelling already petitioned and the alteration of information approved in this petition." (new wording)

Article 44. Failure to comply with the provisions contained in this Resolution constitutes a health infraction, pursuant to Law No. 6,437, of 20 August 1977, without prejudice to the applicable civil, administrative, and criminal liabilities.

Article 45. Paragraph 2 of Article 36 shall be in force in the period of 360 (three hundred and sixty) days from the date this Resolution comes into force.

Article 46. This Resolution shall enter into force 120 (one hundred and twenty) days from the date of its publication. **(This period has been extended by 90 days by Resolution RDC no. 100 of 4 August 2016, revoked by Resolution RDC no. 292 of 24 June 2019)**

JARBAS BARBOSA DA SILVA JR

Director-President

ANNEX I

1. ALTERATIONS RELATED TO THE ACTIVE PHARMACEUTICAL INGREDIENT API manufacturer or API manufacturing site is considered as the company responsible for one or more stages of API manufacture. The API manufacture(s) has/ have the option to send directly to ANVISA, in up to 30 (thirty) days after submission, the documentation related to the API, duly identified with the process number and expedient which is related to.			
Modifications	**Conditions**	**Documents**	**Petitioning type**
a. alteration in API manufacturing site legal name	There should be no alteration in the manufacturing unit in addition to its legal name	1	Immediate implementation. It requires individual submission.
b. replacement or inclusion of manufacturing site of API of the same pharmaceutical group	Synthesis route, production process, batch size, starting material, intermediates, reagents, solvents, and API specifications must remain unaltered.	2, 3, 4, 5, 6, 7, 8, 9, 10	Immediate implementation. It requires individual submission.
c. replacement or inclusion of new API manufacturer	Concomitant alteration of API production process is allowed. Cases of replacement are included or inclusion of manufacturing site of API of the same pharmochemical group, when it does not fit in the specific subject of item "b".	2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14, 15, 17	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation.
d. API production minor alteration	There must be no significant alteration in the qualitative and quantitative profile of impurities (no new impurity above 0.10%, no alteration in the total limit of impurities approved and residual solvents within the limits adopted in official compendia), as well as	4, 5, 6, 7, 10, 14, 16	Immediate implementation. It does not require individual submission. PCH.

	alteration of physicochemical properties. The synthesis route must remain unaltered, i.e., the intermediates remain the same and there are no new reagents, catalysts, or solvents used in the process. The specifications of API or intermediaries should remain unaltered.		
e. major alteration in API production	It refers to the alterations that do not fit in the conditions of minor alteration in API production (item "d")	4, 5, 6, 7, 8, 9, 11, 12, 13, 14, 15, 16, 17	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation.
Documentation			
1	Declaration by the manufacturer stating that only the legal name was altered.		
2	List containing the names and addresses of the companies involved in the different stages of manufacture, including particle size reduction, quality control, and API stability.		
3	Copy of the Good Manufacturing and Control Practices Certificate (GMCPC) issued by Anvisa for the active pharmaceutical ingredient, object of marketing authorization, or copy of the inspection request protocol for GMCPC issuance purposes, provided that the latest inspection has been satisfactory. In the case of APIs not included in the marketing authorization priority list and with international manufacturing, this document may be replaced by a Copy of the document confirming compliance with the Good Manufacturing Practices issued by the health authority of the origin country.		
4	Statement that the API process validation was performed.		
5	Physicochemical and microbiological quality control analytical reports issued by the API manufacturer referring to 1 (one) batch manufactured in the approved condition and 1 (one) batch manufactured in the proposed condition, including impurities profile data, distribution and limits of particle size, and polymorphic forms.		
6	API physicochemical and microbiological quality control analytical reports issued by the medicinal product manufacturer referring to 1 (one) batch manufactured in the approved condition and 1 (one) batch manufactured in the proposed condition, including impurities profile data, distribution and limits of particle size, and polymorphic forms.		

~~7~~	~~Physicochemical and microbiological quality control analytical reports issued by the medicinal product manufacturer referring to 1 (one) batch produced with the API manufactured in the approved condition and 1 (one) batch produced with the API manufactured in the proposed condition.~~
~~8~~	~~Validation report of API quality control analytical methods, performed by the medicinal product manufacturer.~~
~~9~~	~~Validation report of medicinal product stability and quality control analytical methods.~~
~~10~~	~~Stability study protocol referring to the first industrial batch or stability study report referring to 1 (one) industrial batch of the medicinal product.~~
~~11~~	~~Stability study report referring to 1 (one) medicinal product batch. For replacement or inclusion of new API manufacturer (item "c"), when there is no alteration in the synthesis route, production process, batch size, starting material, intermediates, reagents, solvents, API specifications, impurities qualitative and quantitative profile, particle size distribution, and crystalline form (polymorphism), including solvates and hydrates, such proof may be replaced by stability study protocol referring to the first industrial batch.~~
~~12~~	~~Technical report containing the following information about the API: a) nomenclature: Brazilian Common Denomination (DCB); b) structure: structural formula, including relative and absolute stereochemistry, molecular formula and relative molecular mass; c) physicochemical properties: physical form of the salt, stoichiometric relationship between the chemical form of API presentation and its pharmacodynamically active component, melting point, solubility, particle size, and pKa; d) name(s) of API manufacturer(s) and its (their) respective address(es); e) document of the origin country official health authority informing the activities authorized for the API manufacturer or declaration by the API manufacturer informing that the country of origin does not have such document; f) synthesis process description: synthesis process flowchart, including molecular formula, chemical structures of starting materials, intermediates and respective nomenclatures, solvents, catalysts, reagents, and the API, including stereochemistry; g) elucidation of structure and other characteristics and impurities: confirmation of structure based on synthesis route and spectral analysis, including molecule infrared spectrum and other analysis necessary for the correct identification and quantification of the molecule(s), and information about potential structural and geometric isomerism, specific optical rotation, refractive index, chirality, potential for the formation of polymorphs, listing its characteristics and of other polymorphs related to the API and its characteristics and information about impurities; h) description of API tests, specification limits, and quality control methods, accompanied by analytical methods validation report; i) API stability study report containing a summary on the types of studies conducted and the results, in accordance with the specific legislation in force, including the results of forced degradation studies and stress conditions and respective analytical procedures, as well as the conclusions about the shelf life or retest date, and j) primary packaging material description.~~

	~~For replacement or inclusion of new API manufacturer (item "c"), major alteration in API production (item "e"), in the case of API regularly authorized at Anvisa, inform the marketing authorization process number and the API marketing authorization number, in replacement of items "b", "f", "g", "i", and "j" of this document.~~
~~13~~	~~Assessment of the impurities comparative profile (between the approved and the proposed conditions), including the verification of the necessity to conduct a impurity qualification study.~~
~~14~~	~~Comparative dissolution profile between the currently approved and the proposed condition. For pharmaceutical forms to which the dissolution profile is not applicable, present *in vitro* performance test comparative between the currently approved and the proposed condition. For alterations "c" and "e", the comparative dissolution profile and other *in vitro* performance tests must be conducted between the proposed condition and the reference medicinal product.~~
~~15~~	~~Relative bioavailability/ bioequivalence study technical report of the medicinal product. When there are no alterations in API physicochemical proprieties with potential impact on bioavailability, this evidence may be dismissed.~~
~~16~~	~~Technical report containing synthesis route description and API manufacturing flowchart, highlighting the proposed alteration and respective controls of the manufacturing process critical steps.~~
~~17~~	~~Photostability study report.~~

ANNEX 1

1. ALTERATIONS RELATED TO THE ACTIVE PHARMACEUTICAL INGREDIENT (Wording given by Resolution – RDC no. 361 of 27 March 2020)

The marketing authorization holder is responsible for assessing the adequacy of the API specification to the maximum daily dose, route of administration, and pharmaceutical form of the medicinal product subject to post-marketing authorization.

For an API that does not fall within the scope of the Collegiate Board Resolution – RDC establishing the DIFA and the CADIFA, replacing documents 1, 2, 3 and 4, the documentation required in a specific regulation must be submitted, as applicable.

Alterations	Conditions	Documents	Type of petitioning
REPLACEMENT OR INCLUSION OF NEW DIFA WITHOUT CADIFA			
a. inclusion or replacement of new DIFA without CADIFA	Alterations related to tests, specifications limits, and analytical methods of quality control and stability of the active pharmaceutical ingredient and of the medicinal product are allowed simultaneously, due to the alteration proposed. It refers to: – replacement or inclusion of a new DIFA holder without CADIFA; – inclusion of DIFA holder manufacturing process approved with substantially different synthesis route or manufacturing conditions;	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11.	Requires individual filing. It must await a favorable manifestation from Anvisa for implementation.

	– inclusion of intermediate or API manufacturing site of approved DIFA holder with substantially different synthesis route or manufacturing conditions. If the petition is granted, the CADIFA will be issued and the process will be linked to the CADIFA. Petition approval is conditional on the valid API GMP certificate and CADIFA.		
ALTERATIONS OF DIFA WITHOUT CADIFA They refer to alterations to the previously approved DIFA without CADIFA. The following alterations require a new DIFA and, therefore, must be submitted according to the alteration "a. inclusion or replacement of new DIFA without CADIFA": – Inclusion of manufacturing process with substantially different synthesis route or manufacturing conditions; – Inclusion of intermediate or API manufacturing site with substantially different synthesis route or manufacturing conditions. When the alteration of the DIFA without CADIFA refers exclusively to tests, analytical methods, and/ or acceptance criteria of the API and that, in turn, determines an alteration in tests, analytical methods, and/ or specification limits of the API by the medicinal product marketing authorization holder, the DIFA alteration may be concomitant with the alteration of item "2. Alterations Related to Testing, Specification Limits, and Analytical Methods of Quality Control and Stability of the Active Pharmaceutical Ingredient and the Medicinal Product" in Annex I of this Resolution. For DIFA alterations not provided for in ANNEX II of the Collegiate Board Resolution – RDC establishing the DIFA, the classification must be done considering the conditions of alterations "b", "c", "d", and "e".			
	Other administrative alterations are allowed concomitantly.		

b. Administrative alteration of the DIFA without CADIFA (immediate implementation)	1. The alteration is exclusively administrative. 2. It refers to the following administrative alterations of the Collegiate Board Resolution – RDC establishing the DIFA: 1.2, 1.4 and 1.5.	12	Immediate implementation. Requires individual filing.
c. Alteration of DIFA without CADIFA (PCH)	It refers to the following administrative alterations of the Collegiate Board Resolution – RDC establishing the DIFA: 1.3, 1.6 and 1.7. It refers to the following quality alterations of the Collegiate Board Resolution – RDC establishing the DIFA: 2.1.1, 2.1.2, 2.1.3, 2.4.1, 2.5.1, 2.5.2, 2.6.1, 2.6.2, 2.6.4, 2.6.7, 2.6.9, 2.7.1, 2.7.3, 2.7.5, 2.8.1, 2.8.2, 2.8.3, 2.9.1, 2.9.3, 2.10, 2.11.1, 2.11.2, 2.12.1, 2.12.2, 2.12.3, and 2.12.4. 1. There is no alteration in the synthesis route, including starting materials, solvents, reagents, intermediates, and purification/ isolation steps.	12	Immediate implementation. It does not require individual filing. PCH.

	2. There is no impact on the impurities profile and in the API specification. The acceptance criterion restriction is an exception of the condition. 3. For a sterile API, the alteration is not related to the sterilization step. 4. The DIFA alteration does not require an alteration in the medicinal product release or stability specification. The medicinal product acceptance criterion restriction is an exception of the condition. 5. Regarding the API physical properties: 5.1 There is no impact on the physical properties of the API (polymorphism, particle size distribution, morphology); or 5.2 The physical properties of the API do not constitute a relevant quality attribute, considering the pharmaceutical form or manufacturing process of the medicinal product.		

d. Alteration of the DIFA without CADIFA (immediate implementation)	Alterations related to tests, specifications limits, and analytical methods of quality control and stability of the active pharmaceutical ingredient and of the medicinal product are allowed concomitantly, due to the alteration proposed. It refers to the following quality alterations of the Collegiate Board Resolution – RDC establishing the DIFA: 2.2.1, 2.2.2, 2.3.1, 2.3.2, 2.3.3, 2.3.4, 2.3.5, 2.4.2, 2.5.3, 2.6.3, 2.6.8, 2.7.2, 2.7.7, 2.7.8, 2.7.9, 2.9.2, 2.15, 2.16.2, 2.17.1, and 2.17.2. 1. There is no impact on the API impurities profile and specification. The acceptance criterion restriction and inclusion of test is an exception of the condition. 2. For sterile API, the alteration is not related to the sterilization step. 3. The alteration in API does not require an alteration in the specification of medicinal product release or stability. The medicinal product acceptance criterion	2, 3, 5, 6, 7, 12	Immediate implementation. Requires individual filing.

	restriction is an exception of the condition.		
e. Alteration of DIFA without CADIFA (major)	Alterations related to tests, specifications limits, and analytical methods of quality control and stability of the active pharmaceutical ingredient and of the medicinal product are allowed concomitantly, due to the alteration proposed. It refers to the following quality alterations of the Collegiate Board Resolution – RDC establishing the DIFA: 2.1.4, 2.2.3, 2.4.3, 2.4.4, 2.4.5, 2.6.5, 2.6.6, 2.7.4, 2.7.6, 2.13.1, 2.13.2, 2.14, and 2.16.1. 1. The alteration is not classified as "1b", "1c", or "1d". Approval of the petition is conditional on valid API GMP certificate.	2, 3, 5, 6, 7, 8, 9, 10, 11, 12	Requires individual filing. It must await a favorable manifestation from Anvisa for implementation.
	Alterations related to tests, specifications limits, and analytical methods of quality control and stability of the active pharmaceutical ingredient and of the medicinal product are allowed concomitantly, due to the alteration proposed.		

f. Alteration of DIFA without CADIFA (major with migration to CADIFA)	1. The alteration is not classified as "1b", "1c", or "1d". 2. This alteration is alternative to alteration "1e". If the petition is granted, the CADIFA will be issued and the process will be linked to the CADIFA. Petition approval is conditional on valid API GMP certificate and CADIFA.	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11	It requires individual filing. It must await a favorable manifestation from Anvisa for implementation.
INCLUSION OR REPLACEMENT OF CADIFA HOLDER			
g. Inclusion or replacement of CADIFA holder (immediate implementation)	Alterations related to tests, specifications limits, and analytical methods of quality control and stability of the active pharmaceutical ingredient and of the medicinal product are allowed concomitantly, due to the alteration proposed. 1. There is no impact on the API impurities profile and specification. The API acceptance criterion restriction is an exception of the condition. 2. The alteration in API does not require an alteration in the medicinal product release or stability	2, 3, 4, 5, 6, 7, 13	Immediate implementation. Requires individual filing.

	specification. The medicinal product acceptance criterion restriction is an exception of the condition. Implementation of the alteration is conditional to valid API GMP certificate and CADIFA.		
h. Inclusion or replacement of CADIFA holder (major)	Alterations related to tests, specifications limits, and analytical methods of quality control and stability of the active pharmaceutical ingredient and of the medicinal product are allowed concomitantly, due to the alteration proposed. 1. The alteration is not classified as "1g". Approval of the petition is conditional on valid API GMP certificate and CADIFA.	2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13	It requires individual filing. It must await a favorable manifestation from Anvisa for implementation.
ALTERATIONS OF THE DIFA WITH CADIFA For API manufacturing steps not included in the CADIFA (e.g. micronization or sterilization not performed under the DIFA holder's responsibility), alterations "1b", "1c", "1d", "1e", and "1f" must be used.			
	1. There is no alteration in the synthesis route, including starting materials, solvents, reagents, intermediates, and purification/ isolation steps.		

i. Alteration of API with CADIFA (PCH)	2. There is no impact on the API impurities profile and specification. The acceptance criterion restriction is an exception of the condition. 3. The alteration in API does not require an alteration in the medicinal product release or stability specification. The medicinal product acceptance criterion restriction is an exception of the condition. 4. Regarding the API physical properties: 4.1 There is no impact on the API physical properties (polymorphism, particle size distribution, morphology); or 4.2 The API physical properties do not constitute a relevant quality attribute, considering the medicinal product pharmaceutical form or manufacturing process.	13	Immediate implementation. It does not require individual filing. PCH.
	Alterations related to tests, specifications limits, and analytical methods of quality control and stability of the active pharmaceutical ingredient and of the medicinal		

j. Alteration of API with CADIFA (immediate implementation)	product are allowed concomitantly, due to the alteration proposed. 1. There is no impact on the API impurities profile and specification. The acceptance criterion restriction and inclusion of test is an exception of the condition. 2. The alteration in API does not require an alteration in the medicinal product release or stability specification. The medicinal product acceptance criterion restriction is an exception of the condition. Implementation of the alteration is conditional to valid API GMP certificate and CADIFA.	2, 3, 5, 6, 7, 13	Immediate implementation. Requires individual filing.
k. Alteration of API with CADIFA (major)	Alterations related to tests, specifications limits, and analytical methods of quality control and stability of the active pharmaceutical ingredient and of the medicinal product are allowed concomitantly, due to the alteration proposed. 1. The alteration is not classified as "1i" or "1j".	2, 3, 5, 6, 7, 8, 9, 10, 11, 13	It requires individual filing. It must await a favorable manifestation from Anvisa for implementation.

	Approval of the petition is conditional on valid API GMP certificate and CADIFA.		
LINKING THE CADIFA			
l. Linking the CADIFA.	1. The API manufacturer already approved in the medicinal product marketing authorization process has a valid CADIFA for the same API. 2. The conditions of the API approved in the medicinal product marketing authorization process are identical to those of the API for which CADIFA was granted (manufacturer of API and intermediaries, starting material, synthesis route, manufacturing process, specifications of the API and its intermediates). This alteration is optional. The implementation of the alteration is conditional to a valid API GMP certificate.	2, 3, 4, 13, 14	Immediate implementation. Requires individual filing.
Documentation			
1	Letter from the DIFA holder, on behalf of the medicinal product marketing authorization petitioner and with the DIFA reference number, authorizing the use of the DIFA as part of the analysis of the medicinal product subject of the post-marketing authorization petition.		

2	Statement signed by the technical responsible or designated person attesting that the API manufacture is conducted in accordance with the good manufacturing practices for APIs, from the introduction of starting materials. The statement must be based on good manufacturing practices audits conducted pursuant to the Collegiate Board Resolution – RDC that provides for the general guidelines for good manufacturing practices of medicinal products.
3	Expedient number of the API GMP certificate request, according to the Collegiate Board Resolution – RDC that provides for the certification of good API manufacturing practices. For alterations "1d", "1e", "1j", and "1k", the document applies only to the alteration associated to a new manufacturing site.
4	When there is a DIFA confidentiality restriction, statement from the technically responsible person of the marketing authorization holder or person designated by him/ her that the marketing authorization petitioner has possession of the open part.
5	The impact of the alteration on the medicinal product must be assessed and the evidence to be presented must be determined. If the equivalence of the physical properties and the impurities profile of the API is not demonstrated, tests must be carried out with the medicinal product, proportionally to the potential impact of the alteration. Factors to be considered include characteristics of the API (e.g. SCB classification, occurrence of polymorphism, particle size distribution, morphology) and the relevance of such properties to the medicinal product performance (e.g. pharmaceutical form, release system, manufacturing process). When the technical report of the medicinal product relative bioavailability/ bioequivalence study is submitted, alteration "1e", "1h", or "1k" must be filed.
6	Certificates of analysis issued, or API batch analysis carried out by the API manufacturer(s) (1 batch in the condition approved and 1 batch in the condition proposed).
7	Certificates of analysis issued, or API batch analysis carried out by the medicinal product manufacturer (1 batch in the condition approved and 1 batch in the condition proposed).
8	Assessment of the comparative profile of impurities between the approved and the proposed conditions, including the verification of the need for an impurities' qualification trial.
9	Validation report of the API quality control analytical methods, carried out by the medicinal product manufacturer, where applicable.
10	Validation report of the medicinal product quality control analytical methods, where applicable.

11	Report of the stability study of a batch of the medicinal product. If the alterations in the API quality attributes or impurity profile do not impact the medicinal product stability, the stability study protocol of the first industrial batch of the medicinal product may be submitted, upon technical justification.
12	Documentation regarding the DIFA alteration, according to Annex II of the Collegiate Board Resolution – RDC establishing the DIFA (disregarding the column "Type of alteration"). For alterations for which the column "documents" is not filled or those not provided for in Annex II of the Collegiate Board Resolution – RDC establishing the DIFA, the documentation must be compatible with the nature and complexity of the alteration, considering: 1. Sections of the API documentation directly altered by the alteration; and 2. Sections of the API documentation where evidence must be included to support the alteration.
13	CADIFA or revised CADIFA, with the access statement completed by the DIFA holder on behalf of the medicinal product marketing authorization holder. If the DIFA alteration can be implemented due to deadline expiration, the revised CADIFA does not have to be submitted in the medicinal product post-marketing authorization petition.
14	Statement signed by the technically responsible person of the medicinal product marketing authorization holder, stating that the quality level of the API is the same for which the CADIFA was issued. Quality level is understood as all the information related to manufacturing (manufacturing process, synthesis route), quality control, and packaging.

2. ALTERATIONS RELATED TO TESTS, SPECIFICATION LIMITS, AND ANALYTICAL METHODS OF QUALITY CONTROL AND STABILITY OF THE ACTIVE PHARMACEUTICAL INGREDIENT AND MEDICINAL PRODUCT			
Modifications	**Conditions**	**Documents**	**Petitioning type**
a. inclusion of a new test	It refers to alterations performed by the medicinal product manufacturer.	1, 2, 3, 4	Immediate implementation. It is not required individual submission. PCH.

b. exclusion of a test or obsolete method	It refers to alterations performed by the medicinal product manufacturer.	5, 6	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation.
c. tightening of specification limits	It refers to alterations performed by the medicinal product manufacturer. The tightening must occur within the range of the currently approved limits, maintaining the same analytical method.	7, 8	Immediate implementation. It does not require individual submission. PCH.
d. expansion of specification limits	It refers to alterations performed by the medicinal product manufacturer.	7, 8, 9	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation.
e. minor alteration in analytical method	It refers to alterations performed by the medicinal product manufacturer. It does not apply to biological or microbiological method and neither to the alterations in dissolution conditions (apparatus, mean, speed). It is necessary that at least one of the following conditions is fulfilled: 1 – The alteration must be due to product monograph update in the official compendium that was already used; 2 – The alteration must be within the range provided for in the compendium general chapter to which the method belongs;	4, 8, 10, 11, 12	Immediate implementation. It does not require individual submission. PCH.

	3 – Alteration of non-chromatographic technique to chromatographic technique; 4 – Alteration in the parameters of isocratic chromatographic method, which does not include chemical composition of the column or qualitative composition of the mobile phase.		
f. major alteration in analytical method	It refers to the analytical method alteration, which does not meet the conditions described for minor alteration performed by the medicinal product manufacturer.	4, 8, 10, 11, 12, 13	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation.
g. inclusion of complementary analytical method	It refers to inclusions performed by the medicinal product manufacturer. It refers to the cases in which a new method will be added to the same test, also maintaining the previous method both in quality control and stability.	4, 8, 10	Immediate implementation. It does not require individual submission. PCH.
~~h. alterations performed by the API manufacturer~~ **(Excluded by Resolution – RDC no. 361 of 27 March 2020)**	~~It refers to any inclusion, alteration, replacement, or exclusion of tests, specifications, and analytical methods made exclusively by the API manufacturer.~~	~~14, 15, 16, 17, 18~~	~~Immediate implementation. It does not require individual submission. PCH.~~
Documentation copy			
1	Justification of the test, specification limits, and proposed analytical method.		
2	Copy of the proposed analytical method with respective bibliographic references and/ or copy of the compendium.		
3	Analytical reports of physicochemical and microbiological quality control of the API or the medicinal product referring to 1 (one) batch analyzed with the approved test and 1 (one) batch analyzed with the proposed test.		

4	Validation report of the proposed analytical method.
5	Description of the tests and specification limits approved and proposed and justification for exclusion.
6	Risk assessment data confirming that the test or method is not significant.
7	Description of approved and proposed tests and specification limits, and justification for the specification limits proposed.
8	Analytical reports of physicochemical and microbiological quality control of the API or the medicinal product referring to 1 (one) batch analyzed with the approved methods/ specification limits and 1 (one) batch analyzed with the proposed methods/ specification limits.
9	Risk assessment data confirming that the limit expansion does not impact on the medicinal product quality and safety.
10	Copy of the approved and the proposed analytical methods with respective bibliographic references and/ or copy of compendium.
11	Justification and assessment of the differences between the approved method and the proposed method.
12	Data confirming that the proposed analytical method is at least equivalent to the approved method.
13	In the case of alteration in dissolution conditions, report of the dissolution method development.
14	Justification by the API manufacturer for specifications, when non-compendial.
15	Copy of new specification and/ or new analytical method issued by the API manufacturer.
16	Analytical report issued by the API manufacturer referring to 1 (one) batch analyzed with the new specification, the new method or the new test.
17	Analytical method validation report issued by the API manufacturer.
18	Justification by the medicinal product manufacturer for not performing the alteration in its quality control, when applicable.

3. ALTERATIONS RELATED TO THE TESTS, SPECIFICATIONS LIMITS, AND EXCIPIENT QUALITY CONTROL METHODS			
Modifications	**Conditions**	**Documents**	**Petitioning type**
a. alterations in the excipient quality control	It refers to any inclusion, alteration, replacement, or exclusion of tests, specifications, and analytical methods for the excipient,	1, 2, 3, 4	Immediate implementation. It does not require individual submission. PCH.

	performed by the medicinal product manufacturer.		
Documentation			
1	Description of the test, specification limits, or proposed analytical method; comparison and assessment of the differences between the proposed and the approved, and justification for the alteration with respective bibliographic references and/ or copy of compendium and validation.		
2	Quality control analytical reports of the excipient referring to 1 (one) batch analyzed with the tests, specification limits, and analytical methods approved and 1 (one) batch analyzed with the tests, specification limits, and analytical methods proposed.		
3	For test exclusion, risk assessment data confirming that the test is not significant.		
4	For inclusion or replacement of analytical method, data confirming that the proposed analytical method is at least equivalent to the approved method, when non-compendial.		

4. ALTERATIONS IN DESCRIPTION AND COMPOSITION OF THE MEDICINAL PRODUCT			
Modifications	**Conditions**	**Documents**	**Petitioning type**
a. alteration in format and dimensions of tablets, capsules, suppositories, and ovules	There must be no qualitative and quantitative alteration in composition, average weight, other specifications, and performance characteristics of the product. The concomitant minor alteration in the production process and/ or minor alteration in equipment is allowed, due to the proposed alteration.	1, 2, 3, 4, 5	Immediate implementation. It does not require individual submission. PCH.
b. alteration, exclusion, or inclusion of markings in the pharmaceutical form including marks in high and low relief, except breaklines, and ink printings.	There must be no qualitative and quantitative alteration in composition, average weight, other specifications, and performance characteristics of the product. The	1, 2, 3, 4, 5	Immediate implementation. It does not require individual submission. PCH.

	concomitant minor alteration in the production process and/ or minor alteration in equipment is allowed, due to the proposed alteration.		
c. alteration or inclusion of ink printing	There must be no alteration in average weight, other specifications, and performance characteristics of the product.	1, 2, 3, 5, 8, 10, 12	Immediate implementation. It does not require individual submission. PCH.
d. minor alteration in breakline	It refers to breakline inclusion, exclusion or alteration. There must be no alteration of the other specifications and the performance characteristics of the product. It must be in accordance with the medicinal product dosage. For generic and similar medicinal products, it must be consistent with its reference medicinal product. It does not apply to medicinal products with API concentration lower than 2% per dosage unit. It does not apply to modified release tablets. The concomitant minor alteration in the production process and/ or minor alteration in equipment is allowed, due to the proposed alteration.	1, 2, 3, 4, 5, 13	Immediate implementation. It does not require individual submission. PCH.

e. major alteration in breakline	It refers to breakline inclusion, exclusion, or alteration that does not fit in "d" alteration. The concomitant minor alteration in the production process and/ or minor alteration in equipment is allowed, due to the proposed alteration.	1, 2, 3, 4, 5, 13, 14	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation.
f. minor alteration in excipients for solution pharmaceutical forms	It refers to quantitative alterations in excipients that fit in the limits described in the Annex of excipients – Annex III for solution pharmaceutical forms, without alteration in the specifications of the finished product and the excipients. It does not apply to sterile medicinal products. It does not apply to alterations in excipients with preservative function nor those who influence the formulation performance characteristics, such as those that affect absorption and solubility of the API.	2, 3, 5, 15, 16, 17	Immediate implementation. It requires individual submission.
g. major alteration in excipients for solution pharmaceutical form	It refers to alterations in excipients for the solution pharmaceutical forms not covered in item “f”.	2, 3, 6, 7, 9, 10, 11, 14, 15, 16, 17, 18, 19	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation.
h. minor alteration in excipients for semi-solid pharmaceutical forms	It refers to quantitative alterations in excipients that fit in the limits described in the Annex of excipients	2, 3, 4, 5, 15, 16, 17	Immediate implementation. It requires individual submission.

	– Annex III for semi-solid pharmaceutical forms without alteration in the specifications of the finished product and excipients. It does not apply to sterile medicinal products. It does not apply to alterations in excipients that influence the formulation performance characteristics, such as those that affect absorption, release, and solubility of the API. It does not apply to alterations in excipients with preservative function and that affect particle size distribution.		
i. major alteration in excipients for semi-solids pharmaceutical forms	It refers to alterations in excipients for semi-solid pharmaceutical forms not included in minor alteration (item “h”).	2, 3, 4, 6, 7, 9, 10, 11, 14, 15, 16, 17, 18, 19	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation.
j. minor alteration in excipients for solid pharmaceutical forms	It refers to the quantitative alterations in excipients that fit in the limits described in the Annex of excipients – Annex III for solid pharmaceutical forms without alteration in the specifications of the finished product and excipients. It does not apply to alterations in excipients that influence the formulation performance characteristics, such as those that	2, 3, 4, 5, 15, 16, 17	Immediate implementation. It requires individual submission.

	affect absorption and solubility of the API.		
k. major alteration in excipients for solid pharmaceutical forms	It refers to alterations in excipients for solid pharmaceutical forms not included in minor alteration (item "j").	2, 3, 4, 6, 7, 9, 10, 11, 14, 15, 16, 17, 18, 19	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation.
l. alteration in excipients for the other pharmaceutical forms	It refers to alterations in excipients for the pharmaceutical forms not covered in the other items.	2, 3, 4, 6, 7, 9, 10, 11, 14, 15, 16, 17, 18, 19	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation.
m. alteration in excipients responsible for color and flavor	It refers to exclusion or quantitative and/ or qualitative alteration in excipients responsible exclusively for coloring and/ or flavoring an already authorized formulation, without alteration in the specifications of the finished product and excipients in addition to the ones related to the alteration described. This alteration cannot influence the performance characteristics of the formulation, such as API absorption and solubility.	2, 3, 6, 7, 9, 10, 11, 15, 16, 18, 19	Immediate implementation. It requires individual submission.
n. inclusion of new presentation due to flavor alteration	It refers to the inclusion of a new presentation through the addition of excipients responsible exclusively for coloring and/ or flavoring an already authorized formulation without alteration in the specifications of the finished product and excipients in	2, 3, 6, 7, 9, 10, 11, 15, 16, 18, 19	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation. If there is no interest in maintaining the previous presentation, the presentation cancellation must be petitioned.

	addition to the ones related to the alteration described. This alteration cannot influence the performance characteristics of the formulation, such as API absorption and solubility.		
Documentation			
1	Description of specifications related to the approved and proposed alteration.		
2	Discussion on the differences between the approved and proposed production processes, highlighting the potential impact on product performance.		
3	Analytical reports of physicochemical and microbiological quality control of the medicinal product referring to 1 (one) batch manufactured with the approved condition and 1 (one) batch manufactured with the proposed condition. In the case of solutions, it must contain tests such as viscosity, pH, and osmolarity (items “f” and “g”).		
4	Comparative dissolution profile between the currently approved and the proposed conditions. In the case of items “d” and “e”, comparative dissolution profile between the currently approved condition with the whole tablet and new condition with whole and broken tablet. For pharmaceutical forms in which the dissolution profile is not applicable, present *in vitro* performance test comparative between the currently approved and the proposed conditions. For alterations “e”, “i”, “k”, “l”, the comparative dissolution profile and other *in vitro* performance tests must be conducted between the proposed condition and the reference medicinal product.		
5	Stability study protocol referring to the first industrial batch or stability study report referring to 1 (one) industrial batch of the medicinal product.		
6	Stability study report referring to 1 (one) batch of the medicinal product. The company must include in the PCH a long-term stability study report of 3 (three) batches of the medicinal products, being 1 (one) batch presented in this petition and the 2 (two) first industrial batches produced after approval and implementation of the alteration. In the case of alteration in the excipients responsible for color and flavor and inclusion of new presentation due to flavor alteration (items m and n), the company must include in the PCH a long-term stability study report of 2 (two) batches of the medicinal products, being 1 (one) batch presented in this petition and the first industrial batch produced after approval and implementation of the alteration. If the alteration results in exclusion or reduction of excipients responsible for color and flavor, the company may present a stability study protocol referring to the first industrial batch instead of the report.		

7	Photostability study report.
8	Description of ink components and proof of its pharmaceutical use.
9	Discussion on the excipient choice and compatibility data between the medicinal product components, the new excipients, and packaging.
10	Specifications of excipients whose information are still not listed in the marketing authorization, accompanied by tests, specification limits, description of analytical methods, quality control analytical report, and respective bibliographic references and/ or copy of compendium.
11	In the case of excipients used for the first time in a medicinal product or in a new administration route, present documents with manufacture details, characterization, and controls with bibliographic reference to support safety data.
12	Assessment of ink interference in the analysis method of the finished product.
13	Data that demonstrate the equivalence between specifications and performance characteristics of the approved and the proposed medicinal products, both related to the whole tablet and the broken one. In the cases of breakline exclusion, this evidence may be waived.
14	Technical report of relative bioavailability/ bioequivalence study. In the case of major alteration in breakline (item “e”), the company may present a justification for such absence. In the case of major alteration for solids (item “k”), if the alteration is classified as moderate in accordance with the terms of Annex III, this evidence may be waived.
15	Production order and comparative chart "A" of Annex IV.
16	Process validation protocol. For sterile medicinal products, the company must also present a summary of the sterilization process validation report.
17	Results and discussion on the preservative system efficacy test and assessment of the antioxidant system, when these are used in the formulation.
18	Additional information for excipients of animal origin in accordance with the specific legislation in force about the control of Transmissible Spongiform Encephalopathy.
19	Validation report of analytical methods of quality control and stability of the medicinal product. For item “m”, if the alteration results in exclusion or reduction of excipients responsible for color and flavor, this evidence may be waived.

5. ALTERATIONS RELATED TO THE SITE OF ONE OR MORE STAGES OF THE MEDICINAL PRODUCT PRODUCTIVE PROCESS			
Modifications	**Conditions**	**Documents**	**Petitioning type**

a. alteration in the manufacturing site legal name	There must be no alteration in the manufacturing unit in addition to its legal name	1	Immediate implementation. It requires individual submission.
b. inclusion or replacement of secondary packaging site		2	Immediate implementation. It requires individual submission.
c. inclusion or replacement of primary packaging site	It refers to the alterations related to inclusion or replacement of primary packaging line site with or without address alteration. It does not apply to sterile medicinal products. The inclusion or concomitant alteration of primary packaging line equipment is allowed. The alteration or concomitant inclusion of secondary packaging site is allowed, when it is the same site as the primary packaging one.	3, 4, 7	Immediate implementation. It requires individual submission.
d. inclusion or replacement of conventional release medicinal product manufacturing site	It refers to the inclusion or replacement of the site of one or more stages, or the totality of the manufacturing process of conventional release medicinal products, with or without address alteration. It does not apply to sterile products. The concomitant minor alteration in the production process, alteration in capacity or equipment automation, inclusion or replacement of quality control site are allowed.	3, 4, 5, 7, 9, 10, 11, 12	Immediate implementation. It requires individual submission.

e. inclusion or minor replacement of modified release medicinal product manufacturing site	It refers to alteration or inclusion of site related to one or more stages or the totality of the manufacturing process of modified release medicinal products, without address alteration. It does not apply to modified release sterile medicinal products. It does not apply to when there is a necessity of relative bioavailability/ bioequivalence study. The concomitant minor alteration in the production process, or minor alteration in equipment, inclusion or replacement of quality control site are allowed.	3, 6, 7, 9, 10, 11, 12, 15	Immediate implementation. It requires individual submission.
f. inclusion or major replacement of modified release medicinal product manufacturing site	It refers to alteration or inclusion of site related to one or more stages or the totality of the manufacturing process of modified release medicinal products, with address alteration. It refers to the cases that do not fit in alteration item "e". The concomitant alteration in the production process, or alteration in equipment, inclusion or replacement of quality control site are allowed.	3, 6, 8, 9, 10, 11, 12, 13	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation.
g. inclusion or replacement of sterile medicinal product manufacturing site	It refers to alteration or inclusion of site related to one or more steps or the totality of the manufacturing	3, 6, 8, 9, 10, 11, 12, 13	It requires individual submission. It must wait for favorable manifestation of Anvisa for

	process of sterile medicinal products, with or without address alteration. It also refers to inclusion or replacement of primary packaging site for sterile medicinal products. It does not apply to modified release sterile medicinal products. The concomitant alteration in the production process, or alteration in equipment, inclusion or replacement of quality control site are allowed.		implementation in up to 180 (one hundred and eighty) days for the first manifestation.
h. inclusion or replacement of quality control site	It refers to inclusion or replacement of the site where one or more quality control tests are carried out, for the purposes of batch release and/ or medicinal product stability, and test, specification limits, and method remain unaltered, with or without address alteration.	10, 12, 14	Immediate implementation. It does not require individual submission. PCH.
Documentation			
1	Declaration by the manufacturing company stating that only the legal name has been altered. The marketing authorization update must be carried out only after the regularization of Special Manufacturing Authorization for Brazilian companies or of the GMPC for companies located outside of Brazil.		
2	Copy of the document confirming compliance with the Good Manufacturing Practices issued by the health authority of the country of origin, for the production line in which the medicinal product is manufactured.		
3	Copy of the valid Good Manufacturing Practices Certificate issued by Anvisa, for the production line in which the medicinal product is manufactured.		
4	Stability study protocol referring to the first industrial batch or stability study report referring to 1 (one) industrial batch of the medicinal product.		

5	For semisolid and liquid products in which the active ingredient is present in not dissolved form: assessment of the alterations in particles' morphology and comparative profile of the particle size distribution.
6	Stability study report referring to 1 (one) batch of the medicinal product. A long-term stability study report of 3 (three) batches of the medicinal product must be included in the PCH, being 1 (one) batch presented in this petition and the 2 (two) first industrial batches produced after approval and implementation of the alteration.
7	Summary report of the process validation. At least three batches on an industrial scale must have been validated prospectively and successfully in the proposed site.
8	Process validation protocol. For sterile medicinal products, a summary report of the sterilization process validation must also be presented.
9	Production order and comparative chart "B" of Annex IV.
10	Analytical reports of physicochemical and microbiological quality control of the medicinal product referring to 1 (one) batch manufactured/ analyzed in the approved site and 1 (one) industrial batch manufactured/ analyzed in the proposed site.
11	Comparative dissolution profile between the currently approved and the proposed conditions. For pharmaceutical forms to which the dissolution profile does not apply, present *in vitro* performance test comparative between the currently approved and the proposed conditions, in replacement of this evidence. For alterations "f" and "g", the comparative dissolution profile and other *in vitro* performance tests must be conducted between the proposed condition and the reference medicinal product.
12	Validation report of medicinal product quality control and stability analytical methods.
13	Technical report of relative bioavailability/ bioequivalence study.
14	Copy of the valid Good Manufacturing Practices Certificate (GMPC) issued by Anvisa, in the case of laboratory installed in pharmaceutical industry. When the inclusion or replacement is not for a pharmaceutical industry, Reblas qualification may be presented. For laboratory installed in international industry, a document must be presented confirming compliance with the Good Manufacturing Practices or equivalent, which confirms compliance with the Good Laboratory Practices.
15	Justification for the absence of relative bioavailability/ bioequivalence study.

6. ALTERATIONS RELATED TO PRODUCTION PROCESS, EQUIPMENT, AND BATCH SIZE OF THE MEDICINAL PRODUCT			
Modifications	**Conditions**	**Documents**	**Petitioning type**

a. minor alteration in the production process	The alterations in non-critical parameters and non-critical process stages are considered as minor alteration or inclusion of the production process. The parameters and critical or non-critical stages are defined in the productive process validation. It does not apply to sterilization stage or parameter.	1, 4, 5, 6, 8, 10, 12	Immediate implementation. It does not require individual submission. PCH.
b. major alteration in the production process	The alterations in critical parameters and critical stages of the process, alteration in the type of production process, such as switching between dry route, wet route, or direct compression, alterations in sterilization parameters, alterations that impact the release system of the active ingredient, or that do not fit in the item “minor alteration in the production process” are considered major alteration or inclusion of the production process The parameters and critical or non-critical stages are the defined in the production process validation. The concomitant minor alteration in equipment and minor inclusion of batch size due to the major alteration in the production process are allowed.	1, 4, 5, 7, 9, 10, 11	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation.

c. inclusion or replacement of primary packaging equipment	It does not apply to sterile products.	3, 6, 8	Immediate implementation. It does not require individual submission. PCH.
d. minor alteration in equipment	It refers to replacement, inclusion, or exclusion of equipment with the same or different design and operation principle of non-critical stages, or with same design and operation principle of critical stages of the production process. It does not apply to alteration or inclusion of equipment used in aseptic processing and in stages that have potential impact on the modified release system. The concomitant alteration in capacity, equipment automation, or minor alteration in the production process due to alteration in equipment is allowed. The stages and equipment considered critical are those defined in the production process validation.	1, 4, 5, 7, 8, 12	Immediate implementation. It does not require individual submission. PCH.
e. major alteration in equipment	It refers to replacement, inclusion, or exclusion of equipment with different design and operation principle, or equipment with different design and the same operation principle of critical stages of the production process.	1, 4, 5, 7, 9, 12	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation.

	The stages and equipment considered critical are those defined in the production process validation. It refers to replacement, inclusion, or exclusion of primary packaging equipment of sterile medicinal products. The concomitant minor alteration in the production process due to alteration in equipment is allowed.		
f. minor inclusion of batch size	It refers to the increase in batch size of immediate-release pharmaceutical forms, decrease in batch size of all pharmaceutical forms, and batch size increase by up to 10 (ten) times the reference batch size of modified-release medicinal products and specialized pharmaceutical forms. Reference batch is the last batch used to confirm safety and efficacy shown through pharmaceutical equivalence, bioequivalence, and clinical trials, accordingly. It does not apply to medicinal products of active concentration lower than 2% (two percent) in relation to the formula, per dosage unit, except for solutions. It does not apply to oral solid medicinal products whose reference batch size is smaller than 100,000	2, 4, 5, 7, 8	Immediate implementation. It does not require individual submission. PCH.

	(one hundred thousand) pharmacotechnical units or 10% (ten percent) of the batch size produced on an industrial scale, whichever is greater. The concomitant minor alteration in the production process and alteration in capacity and/ or equipment automation is allowed, provided that such alteration is due to the inclusion of batch size.		
g. major inclusion of batch size	It refers to the increase in batch size not included in the item “minor inclusion of batch size”. The concomitant minor alteration in the production process and alteration in capacity and/ or equipment automation is allowed, provided that such alteration is due to the inclusion of batch size.	2, 4, 5, 7, 9, 11	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation.
Documentation			
1	Production order and comparison chart "B" of Annex IV.		
2	Production order and comparison charts "B" and "C" of Annex IV.		
3	Comparison chart "B" of Annex IV.		
4	Analytical reports of physicochemical and microbiological quality control of the medicinal product referring to 1 (one) batch manufactured in the approved condition and 1 (one) batch manufactured in the proposed condition.		
5	Comparative dissolution profile between the currently approved and the proposed conditions. For pharmaceutical form to which the dissolution profile is not applicable, present *in vitro* performance test comparative between the currently approved and the proposed conditions. For alterations “b” and “g”, the comparative dissolution profile and other *in vitro* performance tests must be conducted between the proposed condition and the reference medicinal product.		

6	Stability study protocol referring to the first industrial batch or stability study report referring to 1 (one) industrial batch of the medicinal product.
7	Stability study report referring to 1 (one) batch of the medicinal product. For major alteration in the production process (item “b”) and major alteration in equipment (item “e”), the company must include in the PCH a long-term stability study report of 3 (three) batches of the medicinal product, being 1 (one) batch presented in this petition and the 2 (two) first industrial batches produced after approval and implementation of the alteration. For minor alteration in equipment (item “d”), in the case of replacement or inclusion of equipment of the same design and operation principle, this evidence may be replaced by a stability study protocol referring to the first industrial batch. For minor inclusion of batch size (item “f”), in the case of increase or reduction in batch size by up to 10 times the size of the reference batch, this evidence may be replaced by a stability study protocol referring to the first industrial batch.
8	Summary report of process validation. At least three batches in industrial scale must have been validated prospectively and successfully in the proposed site. For minor alteration in equipment (item “d”), present similarity study for the equipment involved.
9	Process validation protocol. For sterile medicinal products, the company must also present a summary report of the sterilization process validation.
10	Results and discussion on the effectiveness test of the preservative system and assessment of the antioxidant system, when these are used in the formulation.
11	Technical report of the relative bioavailability/ bioequivalence study. For major alteration in the production process (item b), in the case of alterations or inclusions of production that do not impact the active ingredient release system or do not alter the type of production process, this evidence may be replaced by technical justification for absence.
12	For semisolid and liquids products in which the active ingredient is present in a not dissolved form: assessment of alterations in particles’ morphology and comparative profile of particle size distribution.

7. ALTERATIONS RELATED TO THE PACKAGING OF THE MEDICINAL PRODUCT			
The alterations related to fractionable packaging must meet the provisions given by the specific legislation in force, in addition to the provisions in this table. The concomitant alteration of the equipment used exclusively for the packaging process is allowed. If the alteration related to packaging implies alterations related to specification limits and analytical method, the provisions on packaging quality control must be observed.			
Modifications	**Conditions**	**Documents**	**Petitioning type**
a. inclusion of new type of primary packaging	As an example, blister and bottle are considered different types of	1, 3, 4, 5, 6, 7, 8, 11, 12, 13	It requires individual submission. It must wait for favorable

	packaging. If there is no interest in maintaining the previous packaging, the holder must request the marketing authorization cancellation of the presentation(s) in the technical justification.		manifestation of Anvisa for implementation.
b. minor alteration in primary packaging composition	It refers to the alteration in composition and the inclusion of primary packaging with different qualitative or quantitative composition of an authorized medicinal product, where there is equivalence or improvement of materials and packaging characteristics in relation to the protective capacity and interaction with the content, without changing packaging type, shape, and dimensions, the quantity/ volume per package, and the presentation description. It does not apply to sterile medicinal products.	1, 3, 4, 5, 6, 10, 11	Immediate implementation. It does not require individual submission. PCH.
c. major alteration in primary packaging composition	It refers to the alteration in composition and the inclusion of primary packaging with different qualitative or quantitative composition of an authorized medicinal product, without changing the type and the quantity/ volume per package. The concomitant minor alteration in form and dimensions of	1, 3, 4, 5, 6, 8, 11	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation.

	primary packaging is allowed, provided that such alteration is due to the major alteration in packaging composition. It includes the cases not classified as minor (item “b”).		
d. minor alteration in primary packaging shape and dimensions	It refers to alteration in shape and dimensions of the primary packaging of an authorized medicinal product, without changing packaging type, composition, quantity/ volume per package and the presentation description. It does not apply to the packaging part that may affect administration, use, safety, and stability of the medicinal product, nor to sterile medicinal products.	1, 6, 9	Immediate implementation. It does not require individual submission. PCH.
e. major alteration in primary packaging shape and dimensions	It refers to alteration in shape and dimensions of the primary packaging of an authorized medicinal product, without changing packaging type, composition, and quantity/ volume per package. It includes the cases not classified as minor (item “d”).	1, 4, 5, 6, 8, 14	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation.
f. alteration in the primary packaging part without contact with the medicinal product	It refers to alteration in the part of the primary packaging that is not in contact with the authorized medicinal product. It does not apply to the primary packaging part that may affect administration, use, safety, and stability of the medicinal product.	1	Immediate implementation. It does not require individual submission. PCH.

g. minor alteration in secondary packaging or intermediary wrapping	It refers to alteration, inclusion, or exclusion of secondary packaging or intermediate wrapping of an authorized medicinal product, without alteration in presentation description. Alteration in labelling information that does not need previous approval by Anvisa is allowed. It does not apply to functional packaging that can affect administration, use, safety, and stability of the medicinal product.	2, 12	Immediate implementation. It does not require individual submission. PCH.
h. major alteration in secondary packaging or intermediary wrapping	It refers to alteration, inclusion, or exclusion of secondary packaging or intermediate wrapping of an authorized medicinal product. It includes the cases not classified as minor (item “g”).	2, 6, 12. For functional secondary packaging or intermediary wrapping, include: 5, 8	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation.
i. alteration related to inert material	It refers to alteration of characteristics, inclusion, replacement, or exclusion of inert material in the packaging of an authorized medicinal product, such as desiccants.	12, 15, 16	Immediate implementation. It does not require individual submission. PCH.
j. alteration related to diluent	It refers to alteration of characteristics, inclusion, replacement, or exclusion of a diluent/ reconstituting agent that accompanies an authorized medicinal product.	17, 18, 19, 20, 21, 22	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation.

k. alteration related to accessory	It refers to alteration of characteristics, inclusion, replacement, or exclusion of an accessory for administration or measurement of the medicinal product required dose, which is not part of the primary package. The accessories must obligatorily be in appropriate quantities and graduation considering its dosage, when applicable.	23, 24	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation.
l. alteration related to packaging quality control	It refers to alterations in tests, specification limits, and quality control methods of primary packaging, functional secondary packaging, functional intermediate wrappings, and accessories.	25, 26, 27, 28, 29, 30	Immediate implementation. It does not require individual submission. PCH.
Documentation			
1	Characterization of the new packaging, with description, detailed design, materials composing each part of the packaging, and specifications. Comparison with the previous packaging, when applicable.		
2	Characterization of secondary packaging or intermediate wrapping, with description, detailed design, materials composing the packaging, and specifications. Comparison with the previous packaging, when applicable.		
3	Tests, specification limits, description of analytical methods, analytical certificate of packaging quality control, and respective bibliographic references and/ or copy of the compendium. For minor and major alterations in primary packaging composition (items “b” and “c”), this evidence may be waived if there has been no alteration in quality control.		
4	Evidence that there is no interaction between the packaging and its contents, such as migration of the proposed material components to the content and loss of medicinal product compounds in the package. Comparison with data of the previous packaging, when applicable.		
5	Evidence of packaging protective characteristics, such as permeability to oxygen, carbon dioxide, humidity, light transmission. Comparison with data of the previous packaging, when applicable. For minor alteration in primary		

	packaging composition (item “b”) and major alteration in secondary packaging or intermediate wrapping (item “h”), these results must confirm equivalent or greater protection.
6	Data that confirm the equivalence between the approved packaging and the proposed packaging, regarding administration, use, safety, and stability of the medicinal product, when applicable.
7	Discussion on the differences between the packaging stage of the approved and the proposed production processes.
8	Stability study report referring to 2 (two) batches of the medicinal product. The company must include in the PCH a long-term stability study report of 3 (three) batches of the medicinal product, being 2 (two) batches presented in this petition and the first industrial batch produced after approval and implementation of the alteration. For major alteration in shape and dimensions of the primary packaging (item “e”), when there is no alteration in the dead space or surface/ volume ratio, this evidence may be replaced by stability study protocol referring to the first 2 (two) industrial batches.
9	Stability study report referring to 1 (one) batch of the medicinal product, when there is alteration of the dead space or surface/ volume ratio.
10	Stability study protocol referring to the first industrial batch or stability study report referring to 1 (one) industrial batch of the medicinal product.
11	Photostability study report.
12	Layout of the new packaging and package insert leaflet text, when applicable.
13	Validation process summary report. For sterile packaging, declaration that the packaging sterilization process validation was performed, when applicable.
14	For sterile medicinal products, process validation summary report. For sterile packaging, declaration that the packaging sterilization process validation was performed, when applicable.
15	Characterization of the material and its packaging.
16	Results of studies confirming the need for its alteration, inclusion, or exclusion.
17	For alteration in the characteristics of a diluent, documentation required for the post-marketing authorization alteration, in accordance with the provisions in Article 12 and its paragraphs.
18	For inclusion or substitution of a diluent, marketing authorization number of the diluent/ reconstituting solution. In case the diluent/ reconstituting solution has no marketing authorization of its own at Anvisa, the company must present documentation of the diluent marketing authorization, according to the regulatory category in which the diluent is classified, in substitution of this evidence, as for example, specific medicinal product. If the diluent does not fit in the existing regulatory categories, present the documentation provided for in the item Administrative

	Technical Documentation and of the Resolution Quality Documentation for the Marketing Authorization for New, Generic, and Similar Medicinal Products.
19	For inclusion or substitution of a diluent, discussion on the diluent choice, with information on its suitability and safety and efficacy for use in the pharmaceutical form and intended administration route.
20	For inclusion or substitution of a diluent, compatibility studies of the medicinal product with diluent and packaging.
21	For inclusion or substitution of a diluent, stability study report after preparation, referring to at least 1 (one) batch of the diluent.
22	For exclusion of a diluent, justification for the exclusion and definition of alternative means to obtain the diluent as required for the use of the medicinal product.
23	For accessory alteration or inclusion, description and design of the device and evidence that it is compatible and suitable for administration or measurement with accuracy and precision, according to the dosage, and comparison with the previous accessory, when applicable.
24	For exclusion of accessory, justification for exclusion and evidence that the medicinal product can be administered with accuracy and precision in the absence of the device.
25	Description and justification for the test, specification limits, and proposed analytical method.
26	For alteration, inclusion, or replacement of analytical method, assessment of the differences between the approved and the proposed methods.
27	Packaging quality control analytical reports referring to 1 (one) batch analyzed with the tests, specification limits, and analytical methods approved and 1 (one) batch analyzed with the tests, specification limits, and analytical methods proposed.
28	For inclusion or substitution of test and alteration, inclusion, or replacement of analytical method, copy of the approved and the proposed analytical methods with respective bibliographic references, copy of the compendium, and validation, if applicable.
29	For exclusion of test, risk assessment data confirming that the test is not significant.
30	For replacement of test, alteration, inclusion, or replacement of analytical method, data confirming that the proposed analytical method is at least equivalent to the approved method.

8. INCLUSION OF NEW PRESENTATION			
Modifications	**Conditions**	**Documents**	**Petitioning type**

a. inclusion of new presentation	It refers to the inclusion of new presentation with different volume/ weight or number of pharmacotechnical units for an authorized medicinal product, maintaining the type and composition of the authorized packaging material. If there is no interest in maintaining the previous presentations, the holder must request the marketing authorization cancellation of such presentations on the technical justification. The new presentation must be consonant with the medicinal product posology and treatment duration. For the inclusion of new fractionable presentation, the provisions in specific legislation in force are applied, in addition to the provisions in this table. The concomitant minor alteration in shape and dimensions of the primary packaging is allowed.	1, 2, 3, 4, 5	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation.
Documentation			
1	Justification for the new presentation, indicating that this is consonant with the medicinal product's approved dosage and duration of treatment.		
2	Characterization of the new packaging, with description, detailed design, materials composing each part of the packaging, and specifications. Comparison with the previous packaging, when there is an alteration in shape and dimension of the packaging.		

3	Data confirming the equivalence between the characteristics of the approved and the proposed packaging, regarding administration, use, and safety of the medicinal product, when applicable.
4	When there is alteration in volume/ weight, dead space, or surface/ volume ratio, stability study report referring to 2 (two) batches of the medicinal product. The company must include in the PCH a long-term stability study report of 3 (three) batches of the medicinal product, being 2 (two) batches presented in this petition and the first industrial batch produced after approval and implementation of the alteration.
5	For sterile medicinal products, summary report of the process validation, including declaration that the packaging sterilization process validation was performed, when applicable.

9. ALTERATIONS RELATED TO SHELF LIFE OR CONSERVATION CARE OF THE MEDICINAL PRODUCT – It refers to alteration in shelf life or alteration in the conservation care of the finished product and of the product after opened or prepared.			
Modifications	**Conditions**	**Documents**	**Petitioning type**
a. shelf life reduction	It refers to reduction of the shelf life of the finished product and of the product after opened or prepared.	1	Immediate implementation. It requires individual submission.
b. shelf life extension	It refers to extension of the shelf life of the finished product and of the product after opened or prepared.	2	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation.
c. alteration in conservation care	It refers to alteration in the conservation care of the finished product and of the product after opened or prepared. The concomitant alteration in the product's shelf life due to the alteration in conservation care is allowed.	2	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation.
d. alteration in additional storage conditions	It refers to alteration in additional storage conditions.	3	Immediate implementation. It requires individual submission.
Documentation			

1	Long-term or follow-up stability study report referring to 1 (one) batch of the medicinal product, confirming that the medicinal product is not stable in the authorized shelf life.
2	Long-term stability study report referring to 3 (three) batches of the medicinal product, being at least 1 (one) industrial batch. For shelf life extension or alteration in conservation care of the product after opened or prepared, stability study report referring to 3 (three) batches of the medicinal product. For shelf life extension (item "b"), in the cases of prior reduction in shelf life in accordance with the terms of Article 19, the reestablishment of the previous shelf life may be performed upon presentation of a long-term stability study referring to the batch(es) required in the post-marketing authorization petition that originated the reduction, both the ones sent in the referred petition and the ones attached to the PCH.
3	Evidences supporting the alteration, if applicable.

10. INCLUSION OF NEW STRENGTH			
Modifications	**Conditions**	**Documents**	**Petitioning type**
a. inclusion of new strength for new medicinal products	It refers to the inclusion of new strength for a new medicinal product authorized, in the same pharmaceutical form.	1, 2, 3, 5	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation.
b. inclusion of new strength for generic and similar medicinal products	It refers to the inclusion of new strength already authorized in Brazil for an already authorized generic or similar medicinal product, in the same pharmaceutical form.	4	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation.
Documentation			
1	~~Documentation described in sections III and IV of Chapter III of RDC no. 60/2104, which provides for the granting and renewal of marketing authorization for medicinal products with synthetic and semisynthetic active ingredients, classified as new, generic, and similar medicinal products.~~ Documentation described in sections IV and V of Chapter III of Collegiate Board Resolution – RDC no. 200/2017, which provides for the criteria for the granting and renewal of the marketing authorization of medicinal products with synthetic and semisynthetic active ingredients, classified as new, generic, and similar medicinal products, and		

	gives other provisions. If the DIFA is the same one approved for the strength already authorized, presenting the documentation described in Subsection I of Section V of Chapter III of Collegiate Board Resolution – RDC no. 200/2017 is not necessary. **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**
2	Safety and efficacy report in accordance with specific guide, including the results of clinical studies of phase III and phase I and II, if applicable. Clinical studies of phase II and III may be replaced by relative bioavailability evidence when the proposed medicinal product is within the approved therapeutic range. Exceptionally, for a new medicinal product intended to prevention or treatment of serious life-threatening diseases or highly debilitating diseases, the company has the option to present a report of clinical trials containing completed phase II studies and phase III studies started. For the admission of the exceptionality described, the confirmation of unmet medical necessity is mandatory. In specific cases where phase III studies are not applicable and phase II studies are sufficient to confirm the medicinal product's efficacy and safety, the company may submit the marketing authorization petition after the conclusion of phase II studies.
3	Pharmacovigilance Plan appropriate for the new strength, in accordance with the specific legislation in force. In specific situations related to safety, a Risk Minimization Plan may be required in addition to the Pharmacovigilance Plan.
4	~~Documentation described in sections III and IV of Chapter III and Chapter V of RDC no. 60/2014, which provides for the granting and renewal of marketing authorization for medicinal products with synthetic and semisynthetic active ingredients, classified as new, generic, and similar medicinal products.~~ Documentation described in sections IV and V of Chapter III (GENERAL REQUIREMENTS FOR MARKETING AUTHORIZATION) and Chapter V (SPECIFIC REQUIREMENTS FOR THE MARKETING AUTHORIZATION FOR GENERIC AND SIMILAR MEDICINAL PRODUCTS) of Collegiate Board Resolution – RDC no. 200/2017. **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**
5	Updated Pharmacovigilance Report of the medicinal product, in the case of medicinal products commercialized in other countries.

11. ALTERATIONS RELATED TO DOSAGE, USE EXTENSION, INCLUSION OF NEW ADMINISTRATION ROUTE, NEW THERAPEUTIC INDICATION			
Modifications	**Conditions**	**Documents**	**Petitioning type**
a. inclusion of new dosage for new medicinal products	It refers to alteration in dosage for a new medicinal product already	1, 2, 4, 5	It requires individual submission. It must wait for favorable

	authorized, of the same strength, pharmaceutical form, therapeutic indication, and target population. The dosage alteration applies to the initial marketing authorization holder company.		manifestation of Anvisa for implementation.
b. use extension for new medicinal products	It refers to the increase of the target population for a new medicinal product already authorized for the same therapeutic indication. The use extension applies to the initial marketing authorization holder company only.	2, 3, 4, 5	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation.
c. inclusion of new administration route for new medicinal products	It refers to the inclusion of a new administration route in Brazil for a new medicinal product already authorized, of the same pharmaceutical form, same strength, and same therapeutic indication. The inclusion of a new administration route applies to the initial marketing authorization holder company.	2, 4, 5, 6	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation.
d. inclusion of new therapeutic indication for new medicinal products	It refers to the inclusion of a new therapeutic indication in Brazil, for a new medicinal product already authorized, of the same pharmaceutical form and same strength. The inclusion of a new therapeutic indication applies to the initial marketing authorization holder company.	2, 3, 4, 5	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation.

Documentation	
1	Safety and efficacy report in accordance with specific guide, including the results of clinical trials of phase III, and of phase I and II, if applicable. Exceptionally, for a new medicinal product intended to prevention or treatment of serious life-threatening diseases or highly debilitating disease, the company has the option to present a report of clinical trials containing completed phase II studies and phase III studies started. For the admission of the described exceptionality, the confirmation of unmet medical necessity is mandatory. In specific cases where phase III studies are not applicable and phase II studies are sufficient to confirm the medicinal product's efficacy and safety, the company may submit the marketing authorization petition after the conclusion of phase II studies.
2	Updated package insert leaflet text.
3	Safety and efficacy report in accordance with specific guide, including the results of phase II and III clinical studies. In cases of use extension (item "b") for the pediatric population, the confirmation of efficacy and safety, exceptionally, may be carried out through a phase II study (with clinical outcome(s) that support the rationality of the defined dosage for the pediatric population claimed, provided that the disease course and the API effects are sufficiently similar between this population and the population(s) already approved). In order to confirm similarity between populations, the company must present: a) evidences that the pathophysiology, the natural history of the disease, the API metabolism, and the dose-response relationship are similar; and b) evidences of experience with the same API or others of the same therapeutic class, used for the same disease or related diseases in the population claimed. Exceptionally, for a new medicinal product intended to prevention or treatment of serious life-threatening diseases or highly debilitating disease, the company has the option to present a report of clinical trials containing completed phase II studies and phase III studies started. For the admission of the described exceptionality, the confirmation of unmet medical necessity is mandatory. In specific cases where phase III studies are not applicable and phase II studies are sufficient to confirm the medicinal product's efficacy and safety, the company may submit the marketing authorization petition after the conclusion of phase II studies.
4	Updated Pharmacovigilance Periodic Report of the medicinal product, in accordance with specific legislation in force.
5	Pharmacovigilance Plan appropriate to the alteration in accordance with the specific legislation in force. In specific situations related to safety, a Risk Minimization Plan may be required in addition to the Pharmacovigilance Plan.
6	Safety and efficacy report in accordance with specific guide, including the results of clinical studies of phase III and phase I and II, if applicable. Clinical studies of phase II and III may be replaced by relative bioavailability evidence when the proposed medicinal product is within the approved therapeutic range. Exceptionally, for a new medicinal product intended to prevention or treatment of serious life-threatening diseases or highly debilitating disease, the company has the option to present a report of clinical trials containing completed phase II studies and phase III

	studies started. For the admission of the described exceptionality, the confirmation of unmet medical necessity is mandatory. In specific cases where phase III studies are not applicable and phase II studies are sufficient to confirm the medicinal product's efficacy and safety, the company may submit the marketing authorization petition after the conclusion of phase II studies.

12. ALTERATIONS RELATED TO THE MEDICINAL PRODUCT NAME, MEDICINAL PRODUCT MARKETING AUTHORIZATION CANCELLATION, AND EXCLUSION OF ACTIVE INGREDIENT MANUFACTURING SITE, PRIMARY PACKAGING SITE, SECONDARY PACKAGING SITE, AND/ OR PRODUCT MANUFACTURING SITE			
Modifications	**Conditions**	**Documents**	**Petitioning type**
a. alteration in the medicinal product's trade name	It refers to the alteration in the already authorized medicinal products' trade name, and other specific rules to this petition must be observed.	1	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation.
b. cancellation of marketing authorization for presentation	It refers to the cancellation of the marketing authorization for one or more presentations of the medicinal product.	–	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation.
c. cancellation of marketing authorization	It refers to the cancellation of the marketing authorization for all presentations of the medicinal product.	–	It requires individual submission. It must wait for favorable manifestation of Anvisa for implementation.
d. exclusion of active ingredient manufacturing site, primary packaging site, secondary packaging site, and/ or product manufacturing site		2	Immediate implementation. It requires individual submission.
Documentation			
1	Declaration of product non-commercialization.		
2	List of sites that remain in force, signed by the marketing authorization holder technical responsible officer.		

ANNEX II

REQUEST JUSTIFICATION

Description of request[1]
Reason for request[2]
I declare that no alterations, in addition to the one(s) mentioned above, will be carried out and that the information contained in the package insert leaflet text and labeling text shall be altered in accordance with the request described above. The company, represented by the technical responsible officer, quality assurance responsible officer, and regulatory affairs responsible officer undersigned, attests the veracity of the information provided.
Technical Responsible Officer: Quality Assurance Responsible Officer: Regulatory Affairs Responsible Officer:

1. Report containing the alteration proposal requested by the company.

2. Motivation of the alteration proposed by the company, including the technical argument for the alteration performance. When applicable, the company must attach documentation confirming the motivation.

ANNEX III

EXCIPIENTS

It determines the criteria for the classification of excipient alterations as minor and major alterations.

The calculation to define the level of alteration in excipient must be based on the formulation originally authorized or the last formulation that has already demonstrated safety and efficacy through pharmaceutical equivalence, relative bioavailability/ bioequivalence, and clinical studies, accordingly.

1. Pharmaceutical forms in solution:

Minor alteration:

a) The amount of each excipient in the proposed product may vary in ± 10% of the amount of excipient in the product.

2. Semi-solid pharmaceutical forms:

Minor alteration:

a) The alteration in each excipient cannot exceed 5% of the quantity for this excipient;

b) The sum of alterations in excipients cannot exceed 5%;

c) The quantitative alteration in diluents (q.s.p – vehicle) can occur without restriction to the limit of 5%, if such alteration is necessary due to the quantitative alterations in excipients previously mentioned.

3. Solid pharmaceutical forms:

Solid pharmaceutical forms of immediate and modified release whose excipients are not related to the active ingredient release system

Table I – Solid pharmaceutical forms of immediate and modified release whose excipients are not related to the active ingredient release system

	Minor Alteration Limit (%)	**Moderate Alteration Limit (%)**
1. Diluent	± 5.0	± 10.0
2. Disintegrant		
2.1. Starch	± 3.0	± 6.0
2.2. Others	± 1.0	± 2.0
3. Binder	± 0.5	± 1.0
4. Lubricant		

4.1. Magnesium or *calcium* stearate	± 0.25	± 0.5
4.2. Others	± 1.0	± 2.0
5. Slider		
5.1.Talc	± 1.0	± 2.0
5.2. Others	± 0.1	± 0.2
6. Coating film	± 1.0	± 2.0
7. Additive effect of alterations	< 5.0	< 10.0
8. Solvents (that evaporate during the process)	Quantitative	Qualitative

a) The alteration of each of the excipients and the total additive effect of alterations must be calculated considering excipient alterations expressed as weight/ weight percentage (w/w) of total formulation. The percentages of Table I are based on the premise that the product has been formulated considering the active ingredient with 100% of its power declared on the label. The total weight of the pharmaceutical form must remain within the range originally specified, so that the alteration is considered minor.

b) The limits described in Moderate Alteration must be considered only for the purposes of presentation of relative bioavailability/ bioequivalence study. The non-presentation of the relative bioavailability/ bioequivalence study shall be accepted if the alteration is within the limits established for minor and moderate alteration, and with the respective justification based on tests conducted *in vitro*, functionality, and characteristics of excipients, active ingredient, and formulation.

c) In the case of multi-functional excipients, the requirements of the function whose range is more restrictive must be met.

Solid pharmaceutical forms of modified release whose excipients are related to the active ingredient release system

Table II – Solid pharmaceutical forms of modified release whose excipients are related to the active ingredient release system.

	Minor Alteration Limit (%)	**Moderate Alteration Limit (%)**
1. Medicinal products of narrow therapeutic window	± 5.0	n/a
2. Others	± 5.0	± 10.0
3. Additive effect of alterations	< 5.0	< 10.0*
4. Solvents (that evaporate during the process)	Quantitative	Qualitative

* It only applies to medicinal products that do not have narrow therapeutic window

a) The alteration of each one of the excipients and the total additive effect of alterations on the excipients related to the modified release system must meet the provisions in Table II,

considering alterations of excipients expressed as weight/ weight (w/w) percentage of total sum of the excipients that control the release of active ingredient;

b) The limits described in Moderate Alteration must be considered only for the purposes of presentation of relative bioavailability/ bioequivalence study. The non-presentation of the relative bioavailability/ bioequivalence study shall be accepted if the alteration is within the limits established for minor and moderate alteration, and with the respective justification based on tests conducted *in vitro*, functionality, and characteristics of excipients, active ingredient, and formulation.

ANNEX IV

COMPARATIVE CHARTS

Chart A – Comparison of Formulas							
Pharmaceutical Form							
Strength							
			Previous formula		Proposed formula		Differences between the %
Substance	Number of DCB, DCI, or CAS	Function	Strength in mg	% in the formula	Strength in mg	% in the formula	
Active ingredient							
Excipient 01							
Excipient 02							
Excipient 03							
Excipient 04							
			Average weight =		Average weight =		Σ of alterations in % =

Chart B – Comparison of production processes	
Pharmaceutical Form	
Strength	

		Approved Process		Proposed Process	
List of equipment (including automation, capacity, design, and operating principle)					
Pharmacotechnical process description[1]					
In-process control methodologies with specification					
Approved production flowchart					
Stage[2]	Substance[3]	Unitary Operation	Unitary operation parameters[4]	Equipment	In-process control[5]
Proposed production flowchart					
Stage[2]	Substance[3]	Unitary Operation	Unitary operation parameters[4]	Equipment	In-process control[5]

1. Describe the process in the form of topics, numbering each one of the stages and highlighting the differences between the processes.

2. According to the numbering of the pharmacotechnical process description, identify the critical process stages.

3. Indicate the order of substance addition at the stage where this occurs.

4. Information regarding speed, temperature, time, etc., including identification of critical parameters.

5. Inform which tests that will be conducted and at which stage they will occur.

Chart C – Comparison of batch size	
Pharmaceutical Form	

Strength		
	Mass/ Volume	Pharmacotechnical Units
Size of pilot batch/ biobatch		
Size of batch produced in the inclusion of batch size		