COLLEGIATE BOARD RESOLUTION No. 964 OF 20 FEBRUARY 2025

Establishes the general requirements for carrying out Forced Degradation Studies on medicines containing synthetic and semi-synthetic active pharmaceutical ingredients and defines the parameters for the notification, identification, and qualification of degradation products in these same products.

The Collegiate Board of Directors of the Brazilian Health Regulatory Agency, in the use of the attributions vested in it under Article 15, item III, and Article 7, item III of Law no. 9,782 of 26 January 1999, and Article 187, item VI, Paragraphs 1 and 3 of the Internal Regulation approved by Collegiate Board Resolution – RDC no. 585 of 10 December 2021, adopts the following Collegiate Board Resolution, as decided upon in a meeting held on 19 February 2025, and I, Acting Director-President, determine its publication.

CHAPTER I

INITIAL PROVISIONS

Section I

Objective and Scope

Article 1. This Resolution establishes the general requirements for carrying out Forced Degradation Studies and defines the parameters for the notification, identification, and qualification of degradation products in medicinal products.

Article 2. This Resolution applies to medicinal products containing synthetic and/or semi-synthetic active pharmaceutical ingredient(s) (API) in their composition, including when associated with other APIs.

Sole paragraph. In the case of medicinal products containing synthetic and/or semi-synthetic API(s) associated with other API(s), the criteria and parameters established in this Resolution must be applied only to the synthetic and semi-synthetic API(s).

Article 3. This Resolution does not apply to:

I – isolated APIs;

II – isolated excipients;

III – medicinal products used in the development stages of clinical studies, and

IV – medicinal products that contain, in their composition, only APIs classified as biological/biotechnological, peptides, oligonucleotides, fermentation/therapeutic products, vitamins, minerals, amino acids, proteins and inorganic compounds, semi-synthetic APIs derived from fermentation products, radiopharmaceuticals, plant-based APIs, dynamized APIs, and other atypical APIs.

Paragraph 1. For the purposes of controlling degradation products of the medicinal products specified in the caption of this article, specific tests must be adopted, when available.

Paragraph 2. In the absence of specific tests, mentioned in Paragraph 1, control of those degradation products that present significant toxicity or that generate therapeutic inefficacy must be ensured.

Section II

Definitions

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

I – Mass balance: process of summing the content and levels of degradation products in a stressed sample found to verify how close they add up to 100% of the initial value (non-stressed sample), considering the margin of experimental variability (ICH Q1A, altered);

II – Forced degradation study: study that assists in identifying possible degradation products of the API (isolated and in the presence of excipients) in establishing the degradation pathways and intrinsic stability of the molecule and in validating the indicative stability power of the analytical procedure used (ICH Q1A, altered);

III – Formal stability studies: long-term stability study, in use, post-reconstitution or dilution and monitoring performed on primary or compromise batches in accordance with a prescribed stability protocol to establish or confirm the shelf life of a medicinal product (ICH Q1A, altered);

VI – Liquid phase: condition for conducting the forced degradation study in which the API or medicinal product is solubilized or dispersed (as a suspension) in a suitable liquid medium before exposure to the degrading agent and/or degradation condition;

IV – Original phase: condition for conducting the forced degradation study in which the API or medicinal product is directly exposed to the degrading agent and/or degradation condition, without prior solubilization or dispersion;

VI – Identification: structural characterization of the degradation product (ICH Q3B);

VII – Impurity: any component present in the medicinal product other than the API or an excipient (ICH Q3B);

VIII – Identification limit: value above which a degradation product must have its chemical structure identified (ICH Q3B);

IX – Notification limit: value above which a degradation product must be reported (ICH Q3B);

X – Qualification limit: value above which a degradation product must be qualified (ICH Q3B);

XI – Analytical method indicating stability: validated quantitative analytical method capable of detecting, over time, changes in the chemical properties of the API or medicinal product, or

capable of accurately measuring the content of the API, degradation products, and other components of interest, without significant interference (RDC 318/2019, altered);

XII – Degradation profile: description of the degradation products observed in the API or in the finished product (ICH Q3B);

XIII – Impurity profile: description of the identified and unidentified impurities present in a medicinal product (ICH Q3B);

XIV – Degradation product: impurity resulting from chemical changes in the API that arises during the manufacture and/or storage of the medicinal product due to the effect of factors such as light, temperature, pH and water, or by reaction with an excipient and/or with the primary packaging (ICH Q3B);

XV – Relevant degradation product: degradation product observed in tests performed in quality control or in stability studies at concentrations higher than the notification limit defined in this Resolution or degradation products included in the medicinal product specifications, even if formed at levels lower than the notification limits defined in this Resolution.

XVI – Chromatographic purity: absence of interference in the chromatographic signal of the analyte (RDC 166/2017);

XVII – Peak purity: spectral homogeneity of a chromatographic peak, indicative of its chromatographic purity, with the criteria for concluding whether there is spectral homogeneity and the parameters adopted for calculating purity being defined as previously established for the software used or through scientifically based technical evaluation (RDC 166/2017), and

XVIII – Qualification of degradation products: process of acquiring and evaluating data that establishes the biological safety of a specific degradation product or a given degradation profile at a specified level (ICH Q3B).

CHAPTER II

FORCED DEGRADATION STUDY

Section I

Forced degradation study objectives

Article 5. The forced degradation study objectives are:

I – Obtaining the potential degradation profile of the medicinal product;

II – Providing evidence that a proposed method is indicative of stability;

III – Detection of conditions to which the medicinal product is particularly sensitive, to define the specific care that must be taken in the development, production, handling, and conservation of this medicinal product, and

IV – Determination of the main degradation products for a given degradation route, when possible, to facilitate investigations of possible deviations in product quality.

Sole paragraph. Forced degradation studies are applicable to the methods used in medicinal product stability studies to quantify the API content for quantifying degradation products.

Section II

Prior information

Article 6. Before starting experimental forced degradation studies, prior information must be collected to adapt the design of the forced degradation study that will be used.

Paragraph 1. The documentation sent must include at least a summary of the data collected.

Paragraph 2. The documentation described in Paragraph 1 may be sent separately or as part of sections of the CTD, as long as all the information requested in this section is present.

Section III

Conducting the forced degradation study

Article 7. The forced degradation study must comply with the following technical requirements:

I – conduct the study on at least one batch, on a laboratory, pilot, or industrial scale of the medicinal product; and

II – for comparison purposes, the study must also be performed with the isolated API(s).

Sole paragraph. When different API manufacturers or different synthesis or production routes for the API are used, a technically based risk analysis must be performed to assess the need to perform the forced degradation study with the API(s) obtained from different manufacturers and/or through different processes.

Article 8. The forced degradation study must be performed on at least one of the medicinal product concentrations.

Paragraph 1. When the different medicinal product concentrations have a qualitative difference in formulation, the study must be performed on all concentrations of the product or on the concentration whose formulation contains all the excipients present in the others.

Paragraph 2. When the different concentrations of the medicinal product have quantitative differences that result in different API/excipient ratios, the study must be performed on all concentrations of the product or on the concentration whose API/excipient ratio is most critical, according to technical justification.

Paragraph 3. To comply with Paragraphs 1 and 2, when it is possible to demonstrate that the qualitative and quantitative changes do not impact the degradation profile of the medicinal product, a technical justification may be presented for not performing the study in the additional concentrations of the medicinal product.

Article 9. For fixed-dose combinations, in addition to the studies described above, forced degradation studies must be performed with the associated APIs.

Sole paragraph. When there is data showing that the associated APIs do not interact with each other chemically or physically or when the formulation proposed for marketing authorization promotes complete physical separation between the APIs, the degradation study of the associated APIs may be waived.

Article 10. The forced degradation study must include at least the following experimental conditions in the API(s) and in the finished product:

I – liquid phase: acid; base, oxidant (auto-oxidation, peroxidation, and oxidation catalyzed by transition metals);

II – original phase: heating, humidity, and light (ultraviolet and visible, according to the light source requirements described in ICH Q1B guide or its updates).

Paragraph 1. The specific conditions for evaluating the sample must be adjusted based on the specific API(s) and the type of pharmaceutical form to be studied.

Paragraph 2. The final parameters selected for degradation of the API(s) and the medicinal product must be scientifically justified.

Paragraph 3. If any of the listed conditions cannot be used due to the inherent characteristics of the sample, the physical-chemical properties of the medicinal product, the type of medicinal product, the results of previous studies or other scientific considerations, a technical justification must be presented.

Paragraph 4. In cases where the three oxidation conditions described in item I are not tested, technical justifications must be presented for the oxidation conditions selected for evaluation.

Paragraph 5. Liquid phase studies of the finished product may be waived for medicinal products in solid pharmaceutical form, provided that the studies performed with the API(s), in the liquid phase and in the original phase, and with the medicinal product, in the original phase, are adequate to prove the indicative stability power of the method.

Article 11. Forced degradation studies must be performed under conditions that promote degradation to a sufficient extent to allow assessment of the formation of degradation products.

Paragraph 1. The tests must be performed under conditions that promote degradation greater than the intrinsic analytical variations of the method and, ideally, less than that which would lead to degradation that is not relevant for establishing the potential degradation profile of the API.

Paragraph 2. When the degradation obtained under a specific condition is not sufficient to allow assessment of the formation of degradation products, a technical justification must be presented, based on the degradation parameters applied and the intrinsic stability of the molecule to the degradation condition under assessment.

Paragraph 3. The justifications regarding the degradation parameters referred to in Paragraph 2 must consider scientific criteria that demonstrate that the degradation parameters assessed are sufficient to induce a realistic and predictive extent of degradation of the API and to demonstrate that the proposed analytical methods are indicative of stability.

Article 12. The documentation sent to Anvisa must include at least the indication of the analytical method(s) assessed and a summary of the conditions under which the study was conducted and the experimental results obtained.

Paragraph 1. Representative chromatograms and data demonstrating the efficiency of the chromatographic separation must be sent as part of the experimental results obtained.

Paragraph 2. The study protocol and all raw experimental data, including all chromatograms, must be available at the company and submitted to Anvisa in cases where additional clarification is requested.

Paragraph 3. The documentation described in the caption of this article may be submitted separately, or as part of the CTD sections, provided that all the information requested in this section is present.

Section IV

Assessment of results

Article 13. The chromatograms obtained during the forced degradation study must be assessed to verify the chromatographic purity of the API peak and, when applicable, other peaks of interest.

Paragraph 1. In cases where it is not possible to demonstrate the peak purity of the API and, when applicable, other peaks of interest, the company must demonstrate the selectivity of the method through other appropriate parameters or analytical techniques.

Paragraph 2. Peaks of interest are those attributed to impurities and degradation products used in calculating the API content and peaks attributed to active metabolites.

Article 14. The mass balance of the conditions in which significant degradation occurred must be calculated.

Paragraph 1. In cases where positive or negative mass balances are obtained outside the analytical variation ranges, the company must present detailed technical justifications for the results obtained, with a specific rationale for the specific case.

Paragraph 2. The technical justifications presented must demonstrate that the mass balance deviations obtained do not significantly impact the indicative power of the method's stability and that all relevant impurities are adequately detected and quantified by the proposed method.

Article 15. The technical discussion related to the forced degradation study must also include conclusions on the main degradation pathways of the API(s), the degradation products that will be monitored, and the suitability of the analytical method.

Sole paragraph. The results of the studies must also be used to support the development and validation of the analysis method for the relevant degradation product(s) and for the critical analysis of the medicinal product impurity profile.

Article 16. The documentation sent to Anvisa must include at least a summary of the critical analysis of the results of the forced degradation study, which must be documented.

Paragraph 1. The complete critical analysis must be available at the company and must be submitted to Anvisa in cases where additional clarifications are requested.

Paragraph 2. The documentation described in the caption of this article may be sent separately, or as part of the CTD sections, provided that all the information requested in this section is present.

Article 17. Failure to meet any criterion previously set forth in this Chapter must be technically justified and will be subject to analysis by Anvisa.

CHAPTER III

NOTIFICATION, IDENTIFICATION, AND QUALIFICATION LIMITS OF DEGRADATION PRODUCTS

Article 18. The need for notification, identification, and qualification of degradation product(s) shall be assessed based on the information contained in the Table in the Annex to this Resolution.

Paragraph 1. In the assessment described in the caption of this article, the results of the formal stability studies and the specifications of degradation products proposed for the medicinal product must be considered.

Paragraph 2. To assess the need to notify, identify, and qualify degradation products found in stability studies, the highest concentration of the impurity found in formal stability studies must be considered.

Paragraph 3. The degradation product(s) found in formal stability studies in a percentage above the established notification limits must be reported in the stability study and included in the calculation of total impurities.

Paragraph 4. The degradation product(s) found in the formal stability study or that has a proposed specification in a percentage or corresponding value above the established identification limits must have their chemical structure identified and individual quantification must be performed.

Paragraph 5. The degradation product(s) found in the formal stability study or that has a proposed specification in a percentage or corresponding value above the identification limits and below the qualification limits presenting characteristics that lead to the classification of a potentially toxic product must have its safety profile established through a biological safety assessment.

Paragraph 6. The degradation product(s) found in the formal stability study or that has a proposed specification in a percentage or corresponding value above the established qualification limits must, in addition to complying with the provisions of Paragraph 4, have its safety profile established through a biological safety assessment.

Paragraph 7. The safety profile expressed in Paragraph 5 and Paragraph 6 will be established for those products that meet the provisions of Article 18 and may be determined through mutagenicity assessment, in accordance with ICH Guide M7 (R1) and its updates, and general toxicity studies using validated methodology and in accordance with specific guidance for conducting non-clinical safety studies required for the development of medicinal products.

Article 19. The degradation product may be considered qualified when it meets at least one of the following conditions:

I – the degradation product is a significant metabolite found during studies in humans or animals;

II – the observed quantity and the proposed acceptance limit of a degradation product are in accordance with current monographs of official compendia, referring to the product being analyzed, in the pharmaceutical form and route of administration proposed for use;

III – the exposure is equal to or lower than that expressed in the list published in a specific Normative Instruction and its updates;

IV – the quantity observed and the proposed acceptance limit of a degradation product are adequately justified in scientific literature;

V – for generic and similar medicinal products, when the quantity observed and the proposed acceptance limit for a degradation product are similar to the quantity of the same degradation product observed for a comparator medicinal product that has previously complied with the requirements of this Resolution; or

VI – the quantity observed and the proposed acceptance limit for a degradation product do not exceed the exposure demonstrated in toxicity studies.

Paragraph 1. The company will not be exempted from identifying the qualified degradation product(s).

Paragraph 2. The qualification of a degradation product that is in accordance with the current monograph in an official compendium, referring to the API present in the medicinal product being analyzed or referring to a medicinal product in a pharmaceutical form different from that proposed for registration or in a route of administration different from that proposed for use, will depend on the presentation of a technical justification accompanied, if necessary, by additional experimental data, which demonstrate that the proposed qualification limits do not result in increased risk for the patient;

Paragraph 3. For low-risk medicinal products, regulated by Resolution RDC No. 576 of 11 November 2021, or its updates, which contain synthetic and/or semi-synthetic API(s) in their composition, the qualification of impurities may only be carried out through the modalities provided for in items II and III of the caption of this article.

Article 20. To qualify degradation products in accordance with item V of Article 19, the medicinal product under analysis and the comparator medicinal product must be analyzed using the same analytical method, validated and demonstrably indicative of stability.

Paragraph 1. The reference medicinal product or generic medicinal product or medicinal product similar to the product under analysis may be used as the comparator medicinal product if:

I. it has been previously approved by Anvisa; and

II. it has previously complied with the requirements of this Resolution or the requirements of the standards referred to in Article 25 of this Resolution.

Paragraph 2. The applicant for marketing authorization is responsible for selecting the comparator medicinal product and verifying in advance that the proposed medicinal product meets the legal requirements provided for.

Paragraph 3. The maximum limit proposed for the qualified degradation product must be adjusted based on the level of degradation product observed in the comparator medicinal product and may not be higher than the limit approved for the comparator medicinal product.

Paragraph 4. It shall be up to Anvisa, during the technical analysis of the petition, to verify the suitability of the chosen comparator medicinal product and the proposed qualification limits.

Paragraph 5. In cases where it is found that the comparator medicinal product is not suitable or that the proposed qualification limits are outside the limits approved for the comparator medicinal product, the company shall be instructed to adapt the limit(s) of the specific degradation product(s) or to carry out the qualification through another path, among those described in Article 19.

Article 21. The acceptance limits for each individual degradation product and the total limit of degradation products must be included in the medicinal product release specifications and the stability study, as established in Article 18.

Sole paragraph. The degradation product that exceeds the identification limit must be included in the medicinal product release specifications and the stability study.

CHAPTER IV

FINAL AND TRANSITIONAL PROVISIONS

Article 22. The provisions of this Resolution apply to the following situations:

I – Applications for marketing authorization, regularization, inclusion of a new concentration, and inclusion of a new pharmaceutical form of medicinal products containing synthetic and/or semi-synthetic API(s) in their composition, including when associated with other APIs.

II – Changes related to the composition of the medicinal product containing synthetic and/or semi-synthetic API(s) in their composition, including when associated with other APIs in which a new excipient is included or in which the API/excipient proportions are significantly altered;

III – Changes related to the synthetic and/or semi-synthetic API in which there is an impact on the impurity profile, with the generation of a new impurity to be monitored in the API specification.

Sole paragraph. The need to present identification and qualification data for impurities above the limits specified in Annex I also applies to cases of changes in the specifications of the degradation products of the medicinal product, even if the petition in which the specification change was made was not filed in parallel with the changes described in the caption of this article.

Article 23. Products not yet compliant with this Resolution or the Resolutions revoked in Article 25 must present evidence of compliance when filing the first of the post-marketing authorization changes listed below, in accordance with this Resolution:

I – Changes related to the API that are not immediately implemented according to the current post-marketing authorization changes standard;

II – Changes in the composition of the medicinal product that are not immediately implemented according to the current post-marketing authorization changes standard, except for major changes in the groove;

III – Changes in the production process that are not immediately implemented, according to the current post-marketing authorization changes standard;

IV – Changes related to the packaging of the medicinal product, the expiration date or the storage care of the medicinal product for which a long-term stability study report is requested for 3 (three) batches of the medicinal product;

V – Changes related to the analytical method of quality control or stability for testing the content or degradation products of the medicinal product, which are not immediately implemented, according to the current post-marketing authorization changes standard.

Paragraph 1. The evidence referred to in the caption of this article includes the forced degradation study and the identification and qualification data of the degradation products above the limits presented in this Resolution.

Paragraph 2. The presentation of data generated prior to this Resolution is permitted, provided that they comply with the provisions herein or are supplemented with data and justifications pertinent to their compliance.

Paragraph 3. Anvisa may, at any time, request proof of suitability for medicinal products that have not filed the post-marketing authorization petitions specified in the caption of this article when there is evidence of toxicity or loss of efficacy of the medicinal product.

Article 24. Studies that comply with the standards referred to in Article 25 of this Resolution will be accepted, provided that they are filed within 730 (seven hundred and thirty) days from the effective date of this Resolution.

Article 25. The following are hereby revoked:

I – Collegiate Board Resolution – RDC No. 53 of 4 December 2015, published in the Federal Official Gazette No. 233 of 7 December 2015, Section 1, page 48; and

II – Collegiate Board Resolution – RDC No. 171 of 22 August 2017, published in the Federal Official Gazette No. 163 of 24 August 2017, Section 1, page 51.

Article 26. This Resolution shall come into force on the date of its publication.

RÔMISON RODRIGUES MOTA

Acting Director-President

ANNEX

Limits for notification, identification, and qualification of degradation products in medicinal products

	Maximum Daily Dose [1]	Limits [2,3]
Notification Limits	≤ 1g	0.1%
	>1g	0.05%
Identification Limits	<1mg	1.0% or 5µg TDA, whichever is lower
	1mg-10mg	0.5% or 20µg TDA, whichever is lower
	>10mg-2g	0.2% ou 2mg TDA, whichever is lower
	> 2g	0.10%
Qualification Limits	<10 mg	1.0% or 50µg TDA, whichever is lower
	10 mg-100mg	0.5% or 200µg TDA, whichever is lower
	>100 mg - 2g	0.2% or 3mg TDA, whichever is lower
	>2g	0.15%

1 Maximum amount of API administered per day, according to the dosage indicated in the medicinal product leaflet.

2 Degradation product limits are expressed as a percentage of the active pharmaceutical ingredient or as the total daily administration (TDA) of a degradation product. Lower limits may be appropriate if the degradation product is exceptionally toxic.

3 Higher limits must be scientifically justified.