

COLLEGIATE BOARD RESOLUTION – RDC No. 53 OF 4 DECEMBER 2015(*)

(Published on the Federal Official Gazette no. 233 of 7 December 2015)

(Republished on the Federal Official Gazette no. 234 of 8 December 2015)

Establishes parameters for reporting, identification and qualification of degradation products in medications with synthetic and semi-synthetic active substances, classified as new, generic and similar, among 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 of Law no. 9,782 of 26 January 1999, item V and paragraphs 1 and 3 of Article 58 of the Internal Regulation approved in the terms of Annex I of Collegiate Board Resolution – RDC no. 29 of 21 July 2015, considering the provisions in item III of Article 2, and items III and IV of Article 7 of Law no. 9,782 of 1999, and the Agency's Program for Regulation Process Improvement, created by Administrative Rule no. 422 of 16 April 2008, as decided upon in a meeting held on 19 and 20 November 2015, adopts the following Collegiate Board Resolution, and I, Director-President, determine its publication:

Article 1. This Resolution is hereby approved for the regulation of notification, identification, and qualification of degradation products in medicinal products.

Sole paragraph. This Resolution establishes parameters for the verification of degradation products in medicinal products, in order to elaborate the corresponding degradation profile and to notify, identify, and qualify degradation products throughout the shelf life of medicinal products.

Article 2. The provisions in this Resolution apply to medicinal products with synthetic and semi-synthetic active substances, classified as new, generic, and similar medicinal products.

Paragraph 1. This Resolution does not apply to biological/ biotechnological products, excipients, peptides, oligonucleotides, radiopharmaceuticals, fermentation products and their derivatives, herbal medicinal products, raw products of animal origin, specific medicinal products, medicinal products based on vitamins and/ or minerals associated with each other or isolated, polyaminoacids, medicinal products of simplified notification, as well as products used in development stages of clinical trials.

Paragraph 2. For the purposes of control of degradation products regarding the products specified in paragraph 1, specific tests must be adopted, if any. In case there are no specific tests, control must be ensured for degradation products presenting significant toxicity or that generate therapeutic inefficacy.

Article 3. For the purposes of this Resolution, the following definitions shall be adopted:

I – forced degradation study: study that allows the generation of degradation products through exposure of the active pharmaceutical ingredient and the finished product to stress conditions, such as light, temperature, heat, humidity, acid/ basic and oxidation hydrolysis, among others.

This study allows the development of stability indicative methods with adequate specificity and selectivity, as well providing information on possible degradation routes of a particular product;

II – impurity: any component contained in the pharmaceutical ingredient or finished product that is not the active pharmaceutical ingredient nor the excipient(s);

III – identification limit: value above which a degradation product must have its chemical structure identified;

IV – notification limit: value above which a degradation product must be reported in a stability study or studies;

V – qualification limit: value above which a degradation product must be qualified;

VI – degradation profile: description of the results and analytical activities used in detection, identification, structure elucidation, and quantitative determination of degradation products present in the active pharmaceutical ingredient and the medicinal product;

VII – chromatographic purity of the active pharmaceutical ingredient peak: evidence that there is no interference of excipients, impurities, and degradation products in the chromatographic peak of the active pharmaceutical ingredient;

VIII – degradation products: impurities resulting from chemical alterations arising during manufacture or storage of the medicinal product; and

IX – qualification of degradation products: assessment of the biological safety of an individual degradation product or a given degradation profile at a specified level.

Article 4. The forced degradation profile study must meet the following requirements:

I – conduction of the study in a batch, at a laboratory, pilot, or industrial scale of the medicinal product; and

II – for comparison purposes, the study conduction must be done also with the formulation, the placebo, and isolated and associated active pharmaceutical ingredient(s), in case of associations in fixed dose.

Paragraph 1. The forced degradation profile study must be conducted in all concentrations of the medicinal product.

Paragraph 2. In case of fixed-dose associations, forced degradation studies must also be conducted in isolated and associated active pharmaceutical ingredients, as well as the formulation.

Article 5. The company must present studies submitting the sample to the following forced degradation conditions:

I – heat;

II – humidity;

III – acidic solution;

IV – basic solution;

V – oxidizing solution;

VI – photolytic exposure; and

VII – metallic ions.

Sole paragraph. If the conditions described above cannot be employed due to the inherent characteristics of the sample, or if not applicable, there must be a technical justification for not using any of those conditions.

Article 6. Forced degradation studies must promote degradation to the extent enough to allow the assessment of degradation product formation.

Paragraph 1. The tests must promote degradation higher than 10% (ten percent) and lower than that which would lead to complete degradation of the sample, thereby compromising the test.

Paragraph 2. In tests where degradation is lower than 10% (ten percent), the company must present a solid technical justification.

Paragraph 3. The results of trials shall support the development and validation of the analysis method(s) of the degradation product(s) formed and the critical analysis of the medicinal product degradation profile.

Article 7. A degradation profile critical analysis must include:

I – verification of the chromatographic purity of the active pharmaceutical ingredient peak in the medicinal product; and

II – assessment of the factors that may interfere somehow in the stability of the medicinal product.

Article 8. The tests and the respective results of the forced degradation trials must be reconducted and resubmitted when requested:

I – alterations or inclusions in the synthesis route of the active pharmaceutical ingredient; or

II – qualitative and quantitative alterations of excipient in the composition of the finished product.

Paragraph 1. When there is more than one active pharmaceutical ingredient manufacturer, the forced degradation results must be assessed for each manufacturer.

Paragraph 2. In the case of quantitative alterations in excipient, the degradation profile study and technical justification with rationale may be sent for the utilization of the forced degradation study already conducted with the former formulation, without the need to conduct a new forced degradation study. The technical justification must demonstrate the impossibility to form new degradation products.

Article 9. The need for notification, identification, and qualification of the degradation product(s) during the stability study of the medicinal product must be assessed based on the information in the table below:

	Maximum Daily Dose ¹	Limits ²
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% or 2mg TDA, whichever is lower
	>2g	0.10%
Qualification Limits	>10mg	1.0% or 50µg TDA, whichever is lower
	10mg-100mg	0.5% or 200µg TDA, whichever is lower
	>100mg-2g	0.2% or 3mg TDA, whichever is lower
	>2g	0.15%

Where:

1 – Maximum amount of the active pharmaceutical ingredient administered per day.

2 – Limits of degradation products are expressed as the percentage of the active pharmaceutical ingredient or as the total daily administration (TDA) of a degradation product.

Paragraph 1. The results of the quantification trials of degradation product(s) must have critical assessment in relation to the reduction of the active pharmaceutical ingredient content observed during the stability study(ies) initiated or in progress, in accordance with the specific resolution for the conduction of stability studies.

Paragraph 2. The assessment of the need for notification, identification, and qualification of degradation product(s) must consider the highest concentration of degradation impurity found during the stability study.

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

Paragraph 4. The degradation product(s) with percentage or corresponding value above the identification limits established must have their chemical structure identified and an individual quantification must be performed.

Paragraph 5. The degradation product(s) with percentage or corresponding value above the identification limits and below the qualification limits presenting, in their chemical structure, characteristics that lead to the classification of potentially toxic product must have their safety profile established through biological safety analysis.

Paragraph 6. The degradation product(s) with percentage or corresponding value above the qualification limits established, when presenting in their chemical structure characteristics that lead to the classification of potentially toxic product must, in addition to meeting the

requirements in Paragraph 4, have their safety profile established through biological safety analysis.

Paragraph 7. The safety profile expressed in Paragraph 5 and Paragraph 6 shall be established for those products that meet the provisions of Article 10 and may be determined through genotoxicity assessment and general toxicity studies using validated methodology and in accordance with specific guidance for the conduction of nonclinical safety studies required for the development of medicinal products.

Article 10. The degradation product may be considered qualified when meeting at least one of the following conditions:

- I – the degradation product is a significant metabolite found during studies in humans or animals;
- II – the amount observed and the acceptance limit proposed for a degradation product are properly justified in scientific literature or official compendia; or
- III – the amount observed and the acceptance limit proposed for a degradation product do not exceed the appropriate limit observed in toxicity studies.

Sole paragraph. The company shall not be exempted from identifying the degradation product(s).

Article 11. The acceptance limits for each degradation product individually and the total limit of degradation products must be included in the specifications of stability studies and release of the medicinal product.

Sole paragraph. The degradation product that exceeds the notification limit must be included in the specifications of stability studies and release of the medicinal product.

Article 12. ANVISA may request the start of monitoring of (a) particular degradation product(s) for a period prior to that described in this Resolution, if there is any evidence of toxicity or loss of efficacy of the medicinal product.

~~Article 13. The provisions of this Resolution apply to the marketing authorization for medicinal products or inclusion of new concentration or new dosage form, as well as to post-approval alterations where there is alteration in formula, production process, analytical methodology for content or degradation product analysis, synthesis route, or manufacturing site of the medicinal product, conservation care, or composition of primary packaging.~~

Article 13. The Provisions of this Resolution apply in following situations: **(New wording given by Resolution – RDC no. 171 of 24 August 2017)**

- I – marketing authorization for new, generic, and similar medicinal products; **(New wording given by Resolution – RDC no. 171 of 24 August 2017)**
- II – inclusion of new pharmaceutical form; **(New wording given by Resolution – RDC no. 171 of 24 August 2017)**
- III – inclusion of new concentration; **(New wording given by Resolution – RDC no. 171 of 24 August 2017)**

IV – alterations related to the active pharmaceutical ingredient that do not require immediate implementation, in accordance with the regulation in force on post-marketing authorization alterations; **(New wording given by Resolution – RDC no. 171 of 24 August 2017)**

V – alterations in the composition of the medicinal product that do not require immediate implementation, in accordance with the regulation in force on post-marketing authorization alterations, except major alteration in groove; **(New wording given by Resolution – RDC no. 171 of 24 August 2017)**

VI – alterations in the production process that do not require immediate implementation, in accordance with the regulation in force on post-marketing authorization alterations; **(New wording given by Resolution – RDC no. 171 of 24 August 2017)**

VII – alterations related to the medicinal product's packaging, its shelf life, or its conservation care, for which a long term stability study report is required, referring to 3 (three) batches of the medicinal product; **(New wording given by Resolution – RDC no. 171 of 24 August 2017)**

VIII – alterations related to the quality or stability control analytical method for tests on content or degradation products of the medicinal product, which do not require immediate implementation, in accordance with the regulation in force on post-marketing authorization alterations. **(New wording given by Resolution – RDC no. 171 of 24 August 2017)**

Sole paragraph. For item VIII, only the provisions in articles 3, 4, 5, 6, 7, and 8 of this Resolution are applied. **(New wording given by Resolution – RDC no. 171 of 24 August 2017)**

~~Article 14. This Resolution shall enter into force on 23 December 2015 for all marketing authorizations, inclusions of new concentration, or inclusions of new dosage form.~~

~~Paragraph 1. For medicinal products already authorized with the classifications listed in Annex I, this Resolution shall enter into force on 31 December 2017.~~

~~Paragraph 2. For medicinal products already authorized with the classifications listed in Annex II, this Resolution shall enter into force on 31 December 2019.~~

~~Paragraph 3. For other medicinal products already authorized, this Resolution shall enter into force on 31 December 2020.~~

~~Paragraph 4. The petitions referred to in the caption of this article must include documented evidence of the effective compliance with this Resolution.~~

~~Paragraph 5. The petitions filed with ANVISA up to the effective date of the regulation shall be reviewed in accordance with regulations in force on the date of submission.~~

Article 14. This Resolution shall enter into force on 23 December 2015 for all submissions for marketing authorization, inclusion of new pharmaceutical form, or inclusion of new concentration. **(New wording given by Resolution – RDC no. 171 of 24 August 2017)**

Paragraph 1. The petitions for marketing authorization, inclusion of new pharmaceutical form, and inclusion of new concentration submitted to ANVISA before this Resolution enters into force shall be reviewed in accordance with the regulation in force on the date of submission. **(New wording given by Resolution – RDC no. 171 of 24 August 2017)**

~~Article 15. For the cases provided for in paragraphs 1, 2, and 3 of Article 14, the compliance with this Resolution shall be made through a specific protocol with the relevant documentation.~~

~~Paragraph 1. In case there was no specific protocol up to date this Resolution enters into force, Anvisa may determine the production is suspended until compliant or cancel the marketing authorization for the product.~~

~~Paragraph 2. Post-marketing authorization alterations submitted on the same date of, or after the date of the specific protocol must be in accordance with this Resolution.~~

Article 15 This Resolution enters into force on a phased basis for the medicinal products already authorized. **(New wording given by Resolution – RDC no. 171 of 24 August 2017)**

Paragraph 1. For medicinal products already authorized with the classifications listed in Annex I, this Resolution enters into force on 31 December 2017. **(New wording given by Resolution – RDC no. 171 of 24 August 2017)**

Paragraph 2. For medicinal products already authorized with the classifications listed in Annex II, this Resolution enters into force on 31 December 2019. **(New wording given by Resolution – RDC no. 171 of 24 August 2017)**

Paragraph 3. For other medicinal products already authorized, this Resolution enters into force on 31 December 2020 **(New wording given by Resolution – RDC no. 171 of 24 August 2017)**

Paragraph 4. The petitions for post-marketing authorization alterations submitted to Anvisa within the periods established in Paragraphs 1, 2, and 3 shall be reviewed in accordance with the regulation in force on the date of submission. **(New wording given by Resolution – RDC no. 171 of 24 August 2017)**

Paragraph 5. The medicinal products already authorized that do not submit the post-marketing authorization alterations listed in items IV to VIII of Article 13 of this resolution shall need to comply with this Resolution if requested by Anvisa, pursuant to Article 12. **(New wording given by Resolution – RDC no. 171 of 24 August 2017)**

Article 16. Collegiate Board Resolution – RDC no. 58 of 20 December 2013 is hereby revoked.

JARBAS BARBOSA DA SILVA JR.

Director-President

ANNEX 1

FIRST LEVEL OF THERAPEUTIC CLASSES

AUTOIMMUNOSUPPRESSIVE AGENT

AMEBICIDES, GIARDIACIDES, AND TRICOMONICIDES

AMINOGLICOSIDES

ANTIBACTERIAL

ANTIBIOTIC (ANTIMYCOTIC)

ANTINEOPLASTIC ANTIBIOTICS
ANTIBIOTICS , SYSTEMIC–MED. ASSOCIATION AMONG ANT-INFECC.
ANTIBIOTICS, SIMPLE SYSTEMIC
ANTIRHEUMATICS
ANTIBIOTICS SYSTEMIC -MED. ASSOCIATIONS
ANTI-FUNGALS
ANTIMALARIALS
ANTIMETABOLIC ANALOGS OF PYRIMIDINE
ANTIMETABOLIC ANALOGS OF PURINE
ANTIMETABOLIC ANTAGONISTS OF FOLIC ACID ANTIMYCOTICS
SYSTEMIC ANTIMYCOTICS OF ORAL USE
ANTINEOPLASTICS
CYTOTOXIC ANTINEOPLASTICS
ANTI-INFECTIVES
ANTI-PARASITICS
ANTI-THYROIDS
ANTIVIIRALS
ANTIVIRALS (INHIBITS VIRAL REPLICATION)
CEPHALOSPORINS
CYTOSTATIC, ALKYLATING
CLASS OF TETRACYCLINES
CHLORAMPHENICOL AND ANALOGS
ESTROGENS ASSOC OTHER DRUGS EXCLUSIVE OF ANDROGENS
ESTROGEN, SIMPLE
PHENOXYPENICILLINS
LEPROSTATICS
THYROID HORMONES AND ANTI-THYROIDS
SEXUAL HORMONES EXCLUSIVE OF OXYTOCICS
THYROID HORMONES, SIMPLE OR ASSOCIATED WITH EACH OTHER
IMUNODEPRESSANT
IMMUNOSUPPRESSANT

MACROLIDES
HORMONAL OXYTOCICS
OTHER ANTINEOPLASTICS
OTHER ANTIPARASITICS FOR INTERNAL CONDITIONS
OTHER MEDIATOR HORMONES AND EQUIVALENT PRODUCTS
BROAD-SPECTRUM PENICILLIN
PENICILLIN G AND DERIVATIVES (BENZILPENICILLINS)
PENICILLINASE-RESISTANT PENICILLINS
PRODUCT FOR TREATMENT OF TRICHOMONIASIS
RIFAMPICINS
SULFAS
SIMPLE SULFAS
TRIMETHOPRIM IN ASSOCIATION WITH SULFAS
TUBERCULOSTATICS
TUBERCULOSTATICS AND LEPROSTATICS

ANNEX II

SECOND LEVEL OF THERAPEUTIC CLASSES

BETA BLOCKERS
ANALGESICS FOR MIGRAINE
NON-NARCOTIC ANALGESICS
SIMPLE ANDROGENS
SIMPLE ANXIOLYTICS
ANTIACIDS
ANTIACIDS AND ANTI-ULCER MEDICATIONS
ANTIACIDS AND ANTI-ULCER MEDICATIONS, ASSOCIATED
ANTIACIDS AND ANTI-ULCER MEDICATIONS, SIMPLE
PLATELET ANTIAGGREGANTS
ANTIASTHMATICS

ANTICOAGULANTS
BIRTH CONTROL PILLS
ANTICONSULSANTS
ANTICONSULSANTS AND ANTIPARKINSONIANS
ANTIDEPRESSANTS
ANTIDIABETICS
ANTIGLAUCOMATOSUS
ANTIGOUT MEDICINAL PRODUCTS
ANTIHYPERTENSIVES
ANTIHYPERTENSIVES, SIMPLE
ANTIHYPERTENSIVES-MEDICINAL ASSOCIATIONS
ANTILIPEMICS
ANTIRHEUMATIC ANTIINFLAMMATORIES
ANTIRHEUMATIC ANTIINFLAMMATORIES – MED ASSOC.
ANTIPARKINSONIANS
ANTITHROMBOTICS
ANTI-ULCER MEDICATIONS
BETA BLOCKERS, SIMPLE
NEUROMUSCULAR BLOCKERS
DIURETICS
SIMPLE DIURETICS
SYSTEMIC GLUCOCORTICIDS
SYSTEMIC GLUCOCORTICIDS – MEDICINAL ASSOCIATIONS
CARDIAC GLYCOSIDES
ORAL HYPOGLYCEMICS
CORTICOSTEROID HORMONES
ALPHA-REDUCTASE INHIBITOR
MEDICATIONS WITH ACTION ON THE MYOCARDIUM
NEUROLEPTICS
OTHER ANTI-ASTHMATIC MEDICATIONS
OTHER PRODUCTS WITH CARDIOVASCULAR ACTION

OTHER PRODUCTS WITH ACTION ON MYOCARDIUM AND CONDUCTION SYSTEM

OTHER PRODUCTS THAT ACT ON THE NERVOUS SYSTEM

OSSEOUS REABSORPTION SUPPRESSANTS

CEREBRAL VASODILATORS

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