

HOMOGENEITY TESTING OF FEED INGREDIENTS

Endorsed by the Steering Committee in
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It is recommended for the companies willing to submit applications/dossiers for pre-market authorization, to contact the jurisdictions of the countries concerned to confirm their acceptance of the current guidance document.

The International Cooperation for Convergence of Technical Requirements for the Assessment of Feed Ingredients (ICCF) was launched in 2017 and aims to develop and establish common guidance documents to provide technical recommendations for the assessment of feed ingredients, including new uses of existing feed ingredients.

This guidance document has been developed by the appropriate ICCF Experts Working Group and was subject to consultation by the Parties, in accordance with the ICCF Process.

The founding members of the ICCF include the Canadian Food Inspection Agency (CFIA), the European Commission (DG SANTE), the U.S. Food and Drug Administration (FDA), as well as the American Feed Industry Association (AFIA), the Animal Nutrition Association of Canada (ANAC), the EU Association of Specialty Feed Ingredients and their Mixtures (FEFANA) and the International Feed Industry Federation (IFIF).

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TABLE OF CONTENT

1. INTRODUCTION	4
1.1 Objective of the Guidance.....	4
1.2 Definitions	4
1.3 Scope of the Guidance	6
2. GENERAL PRINCIPLES.....	6
3. HOMOGENEITY TESTING.....	8
3.1 Homogeneity Testing of a Feed Ingredient in Ingredient Market Formulation	8
3.2 Homogeneity Testing of a Feed Ingredient in Premixture	9
3.3 Homogeneity Testing of a Feed Ingredient in Feed	10
3.4 Homogeneity Testing of the Feed Ingredient in Drinking Water for Animals	11
4. SPECIAL CONSIDERATIONS.....	12
4.1 Silage Feed Ingredient.....	12
4.2 Flavoring Agent.....	12
4.3 Colorant	13
5. SAMPLING FOR A HOMOGENEITY TEST.....	13
6. DATA EVALUATION AND STATISTICAL ANALYSIS.....	15
7. DATA REPORTING	15
7.1 The Description of a Homogeneity Test Should Include:	15
7.2 The Analytical Data Should Include:	16
8. BIBLIOGRAPHY.....	16
8.1 AOAC.....	16
8.2 CODEX Alimentarius	17
8.3 VICH	17

8.4 United States of America	17
8.5 European Union	17
8.6 Others	18
9. Abbreviations	19

HOMOGENEITY TESTING OF FEED INGREDIENTS

1. INTRODUCTION

1.1 Objective of the Guidance

This document provides guidance regarding the homogeneity testing approaches and data to be included in a pre-market approval or authorization application for feed ingredients. It is not intended to provide guidance on the testing of the performance of the mixing devices in feed manufacturing facilities.

Considerations in the document are provided for the assessment of the uniform distribution of feed ingredients throughout the feed chain while being incorporated in different intended matrices. This guidance has been developed with an international team of experts and represents the best practices for the provision of meaningful results.

While this guidance supports the acceptability of the testing protocol, applicants are advised to consult the appropriate regulatory authorities or their guidelines during the development phase of new feed ingredients or a new uses of an authorized feed ingredient. This will help to determine whether the testing described herein is acceptable, or if the testing is needed for a specific pre-market approval or authorization.

1.2 Definitions

The following definitions apply solely in the context of this guidance document:

Active substance¹: Any substance in a feed ingredient that contributes to the intended effect.

Batch: An identified quantity of a feed ingredient or intended matrix having uniform characteristics, with specified limits and being produced from the same cycle of manufacturing production.

¹ Active substance includes microorganisms that contribute to the intended effect.

Carrier: A feed ingredient or water used to physically facilitate handling of the feed ingredient under assessment and its incorporation into ingredient market formulations, premixtures, feeds or water. The use of a carrier does not alter the feed ingredient's intended effect and purpose.

Coefficient of variation (CV): A measurement of relative variability. It expresses the standard deviation as a percent of the mean. It is calculated using the formula:

$$CV(\%) = \frac{SD}{\bar{X}} \times 100$$

SD = standard deviation, \bar{X} = mean

Feed (Feedingstuff)²: Any single or multiple materials, whether processed, semi-processed or raw, which is intended to be fed directly to animals.

Feed ingredient²: A component part or constituent of any combination or mixture making up a feed, whether or not it has nutritional value in the animal's diet. Ingredients are of plant, animal, microbial or aquatic origin, or other organic or inorganic substances.

Feed supplement: A feed used with another feed to improve the nutritive balance or performance of the total ration and intended to be:

- Fed undiluted as a supplement to other feeds; or
- Offered free choice with other parts of the ration separately available; or
- Further diluted and mixed to produce the total ration.

Homogeneity: The ability of a feed ingredient to be distributed uniformly throughout an intended matrix.

Homogeneity testing: The assessment of the uniform distribution of a feed ingredient in an intended matrix.

Ingredient market formulation: The feed ingredient under assessment formulated with carrier(s) and/or other feed ingredient(s). It is the commercial product used to incorporate the feed ingredient under assessment into premixtures, feeds or water.

² Adapted from Codex Alimentarius, Code of Practice on Good Animal Feeding (CAC/RCP 54-2004)

Intended matrix: A matrix in which the feed ingredient is added and is used to supply the feed ingredient to the animals. It may include the ingredient market formulation, premixture, feed, feed supplement, and water.

Premixture (Premix): A uniform mixture of one or more feed ingredients with a carrier, not intended for direct feeding to animals. It is used to facilitate uniform dispersion of the feed ingredients in a larger mix.

Representative sample³: A sample in which the characteristics of the batch from which it is drawn are maintained. It is a simple random sample where each of the items or increments of the batch has been given the same probability of entering the sample.

1.3 Scope of the Guidance

This guidance document addresses the homogeneity testing of feed ingredients, when incorporated into their intended matrices.

The types of feed ingredients covered by this guidance in each regulatory jurisdiction are determined by each jurisdiction's relevant statutes and regulations.

2. GENERAL PRINCIPLES

A homogeneity test should evaluate the uniform distribution of the feed ingredient to demonstrate that the active substance(s) it contains can be uniformly distributed under conditions of the proposed use in the intended matrices. For nutritional feed ingredients, this is to ensure the animal's uniform exposure to the feed ingredient and avoid either a nutrient deficiency or overexposure. For feed ingredients having other intended effects in feed, this is to ensure the intended effect can be achieved uniformly. The homogeneity test shall demonstrate that the feed ingredient under assessment can be uniformly distributed in the intended matrix, using mixing equipment that is readily available to a feed manufacturer (see **Section 5**).

Homogeneity test for a feed ingredient should be conducted in the intended matrix at the proposed inclusion level of the feed ingredient. When the intended inclusion level of a feed ingredient in a specific feed matrix is a range of levels, the homogeneity test should be conducted using the minimum intended inclusion level.

³ Adapted from Codex Alimentarius, General Guidelines on Sampling (CAC/GL 50-2004)

When the feed ingredient contains more than one active substance, the need for homogeneity testing for all active substances will depend on their characteristics. If all active substances can be sufficiently identified and quantified, and the concentration/activity of each active substance is guaranteed on the label of the intended matrix, then the uniform distribution of each active substance in that matrix should be demonstrated. However, when it is not practical to identify and quantify all active substances in the intended matrix, it is acceptable to test for the predominant active substance to demonstrate the uniform distribution of the feed ingredient in that matrix. If the predominant active substance cannot be adequately identified and quantified in the intended matrix, a marker compound which is a constituent of the feed ingredient can be tested to support the uniform distribution of the feed ingredient in that matrix.

Following are few examples of feed ingredients containing more than one active substance:

- For a feed ingredient that consists of two different enzymes (e.g. a xylanase and a glucanase), and the activities of both enzymes are indicated on the label of the intended matrix containing the feed ingredient, the homogeneity testing for the feed ingredient in the intended matrix should test for both enzymes by measuring their activities.
- For a feed ingredient that is a chemical substance existing as two isomers in an equilibrium, testing for only one of the isomers in the intended matrix would be acceptable.
- For a feed ingredient that is a botanical extract, the testing for the predominant active substance of the extract would be acceptable to evaluate the uniform distribution of the extract in its intended matrix. If it is not practical to identify and quantify the predominant active substance in the intended matrix, testing on a marker compound which is a constituent of the extract would be acceptable.

The homogeneity test should be based on appropriate sampling procedures (see **Section 5**) to ensure that representative samples are tested. The sampling procedure should consider the physical characteristics of the feed ingredient, the approach to incorporate the feed ingredient into the intended matrix, and the variation of the analytical method(s) used. The test should include a minimum of 10 representative samples that are taken from one batch of the intended matrix being tested (see **Section 5**). The concentration/activity of the active substance(s) of the feed ingredient contained in each sample is measured using an analytical method that is validated to be fit for the analysis. The Coefficient of Variation (CV) should be calculated using

results from all the samples collected to demonstrate the homogeneity (see **Section 6**). Depending on the use level of the feed ingredient in the intended matrix tested, the acceptable CV may vary. For example, if the concentration/activity of the active substance in the intended matrix is in the parts per billion (ppb) range, the acceptable CV for the tested feed ingredient may be higher than the one for a feed ingredient used at a higher inclusion level.

Analytical method(s) used in a homogeneity test should be regulatory or internationally accepted methods for the relevant active substance in the intended matrix. In the absence of such methods, the method of analysis should be validated in all the intended matrices in which the homogeneity of the feed ingredient is intended to be tested. The method validation should follow the protocols recommended by international standards or guidance.

3. HOMOGENEITY TESTING

This section describes the approach to conduct a homogeneity test in each of the intended matrices. The need for a homogeneity test for a feed ingredient in a specific intended matrix and how it should be conducted depend on the characteristics of the feed ingredient and the intended matrix, and conditions of proposed use of the feed ingredient, including the directions for incorporation and the proposed inclusion level in that matrix.

When a feed ingredient is intended to be sold in the form of an ingredient market formulation, this ingredient market formulation should be used to incorporate the feed ingredient at proposed inclusion levels into the matrices, for which the homogeneity test is conducted.

3.1 Homogeneity Testing of a Feed Ingredient in Ingredient Market Formulation

When a feed ingredient is marketed in the form of an ingredient market formulation, a homogeneity test will ensure uniform distribution of the feed ingredient in the ingredient market formulation and adequate incorporation in subsequent intended matrices.

A homogeneity test for a feed ingredient in the ingredient market formulation is recommended but may not be necessary when properly justified.

The following elements should be considered when determining whether a homogeneity test is needed for a feed ingredient in an ingredient market formulation:

- The physical characteristic of the ingredient market formulation. For example, it may be more difficult to evenly distribute a feed ingredient in a viscous

formulation than in a dry free flowing formulation. For a feed ingredient intended to be sold in both liquid and dry formulations, a homogeneity test in each of the liquid or dry ingredient market formulations should be considered.

- The particle size of the feed ingredients and/or the carrier(s) used in the ingredient market formulation. For example, a significant difference in particle size between the feed ingredient under assessment, the carrier(s) and/or other feed ingredient(s) of the ingredient market formulation could cause uneven mixing.
- The intended inclusion level of the feed ingredient in the ingredient market formulation. In general, it is more challenging to uniformly distribute a feed ingredient when the inclusion level in the ingredient market formulation is low.
- The safety profile of the feed ingredient. For certain feed ingredients, its unique safety profile may warrant a homogeneity test to ensure the uniform distribution in the ingredient market formulation. For example, selenium has a very narrow safe and effective working range, i.e. the effective concentration of selenium is very close to the lowest concentration at which selenium becomes toxic. For a feed ingredient intended to be used as a selenium source, a homogeneity test may be needed to ensure the uniform distribution of the ingredient in the ingredient market formulation to avoid safety concerns for animals.

When a homogeneity test for a feed ingredient in the ingredient market formulation is needed, it should be conducted using the ingredient market formulation with the feed ingredient under assessment at the intended inclusion level.

3.2 Homogeneity Testing of a Feed Ingredient in Premixture

When the feed ingredient is intended to be incorporated in a premixture prior to the incorporation into feed, a homogeneity test is recommended to demonstrate that the feed ingredient can be uniformly distributed in the intended premixture. To conduct a homogeneity test in premixture, the feed ingredient should be incorporated into the premixture at the intended inclusion level using mixing equipment that is readily available and commonly used in the feed industry (see **Section 5**). The quantitative and qualitative composition of the premixtures should be provided. It should be representative of usual compositions in the jurisdiction region in which the approval will be sought.

When a feed ingredient is intended to be mixed in premixtures prior to being incorporated into feeds for multiple animal species, the variability of the premixture compositions for the

different animal species should be considered. Therefore, the homogeneity testing for the feed ingredient in these different premixtures should preferably be conducted on a representative ruminant premixture, on a representative monogastric premixture (either swine or poultry), and on a representative premixture for aquaculture species, if the conditions of proposed use include target species that fall under these classifications. A rationale should be provided to justify the choice of the representative premixture compositions.

3.3 Homogeneity Testing of a Feed Ingredient in Feed

A homogeneity test for the feed ingredient in feed is recommended to demonstrate its uniform distribution in feed and to ensure that its intended effect can be achieved uniformly throughout the feed. To conduct a homogeneity test in feed, the feed ingredient should be incorporated into the feed at the intended inclusion level, using mixing equipment that is readily available and commonly used in the feed industry (See **Section 5**). The quantitative and qualitative composition of the feed should be provided. It should be representative of usual compositions in the jurisdiction region in which the approval will be sought.

When a feed ingredient is intended to be used in feed for multiple animal species, testing should preferably be conducted on a representative ruminant feed, on a representative monogastric feed (either swine or poultry), and on a representative feed for aquaculture species, if the conditions of proposed use include target animal species that fall under these classifications. A rationale should be provided to justify the choice of the representative feed compositions.

When a feed ingredient is intended to be incorporated into feed directly without mixing into a premixture first, and the homogeneity test demonstrates a uniform distribution of the feed ingredient in feed, when incorporated directly, a homogeneity test in a premixture according to **Section 3.2** is not necessary.

However, in some cases, it is difficult to achieve uniform distribution of a feed ingredient when the feed ingredient is directly incorporated into feed. For example, the physical characteristics of the feed ingredient and intended feed matrix (e.g. particle size, viscosity) makes it a challenge to uniformly distribute the feed ingredient throughout the feed, or the inclusion level of the feed ingredient is too low for the active substance to be accurately identified and quantified using currently available analytical methods. Under these conditions, a pre-dilution of the feed ingredient, in a premixture prior to the incorporation in feed should be considered. In

this case, the uniform distribution of the feed ingredient in the premixture should be demonstrated according to the recommendations provided in **Section 3.2**.

When a feed ingredient is intended to be used in both mash feed and pelleted feed produced from the same mash feed, a homogeneity test shall be performed in both the mash and pelleted feeds.

For a feed ingredient intended to be used in a liquid feed supplement, if the feed ingredient is soluble/miscible at the proposed use level, the homogeneity test is generally not necessary. Otherwise, as there is a greater possibility of separation of the feed ingredient, a homogeneity test should be conducted at the proposed use level under the conditions simulating practical use. It should be conducted at two time points, preferably at the time of production and at the end of the proposed shelf life of the liquid feed supplement to demonstrate the feed ingredient remains uniformly distributed over the anticipated lifetime of the liquid feed supplements. If the CV from the homogeneity test at the end of the proposed shelf life is significantly higher than that from the initial test, or if the visual or physical inspection demonstrate uneven distribution, labeling instructions for agitation/recirculation of the liquid feed supplement may be needed to ensure the uniform distribution of the feed ingredient over the anticipated lifetime of the liquid feed supplement, either at the time of feeding or during the storage period.

For a feed ingredient intended to be added to milk (fresh milk, dry/dehydrated milk or milk replacing powder reconstituted with water) shortly before feeding to the animals, the homogeneity test can be replaced by the measure of the ability of the feed ingredient to dissolve/disperse in the liquid preparation.

3.4 Homogeneity Testing of the Feed Ingredient in Drinking Water for Animals

For a feed ingredient intended to be administered to animals through drinking water, a homogeneity test is generally not necessary if the feed ingredient is soluble/miscible in water at the proposed use level. Otherwise, a homogeneity test should be conducted to demonstrate that the feed ingredient can be dispersed in water uniformly at the proposed use inclusion level and under specified water conditions simulating practical use (e.g. pH, mineral contents, water temperature, time, microbial contents, dispersion/suspension of the ingredient). If a dispersion/suspension system is used, the homogeneity test should also demonstrate whether the feed ingredient is uniformly dispersed over the anticipated lifetime of the drinking water for animals (typically 48 hours). A test at the end of the anticipated lifetime (e.g. 48 hours) is

acceptable to demonstrate the homogeneous distribution of the feed ingredient over the anticipated lifetime of drinking water for animals.

In the case where the CV is significantly higher at the end of the anticipated lifetime (48 hours) than at the time of introduction of the feed ingredient in drinking water for animals, or if the visual or physical inspection demonstrate uneven distribution, the label instructions should indicate that the drinking water containing the feed ingredient should be used quickly and agitation/recirculation may be needed to ensure the intended effect.

4. SPECIAL CONSIDERATIONS

4.1 Silage Feed Ingredient

The homogeneity test for a silage feed ingredient in the ingredient market formulation and in premixture, if it is intended to be added in a premixture prior to incorporation into silage, should be conducted according to **Sections 3.1** and **3.2**, as appropriate.

For a silage feed ingredient, a homogeneity test in the silo is normally not necessary. The uniform distribution of a silage feed ingredient in the silo may be supported by demonstration of its intended effect.

4.2 Flavoring Agent

The homogeneity test for a flavoring agent in the ingredient market formulation and in premixture should be conducted according to **Sections 3.1** and **3.2**, as appropriate.

For the case of feed or drinking water for animals containing a flavoring agent, when an analytical method is available to quantitatively determine the concentration of a representative constituent of the flavoring agent (the flavoring substance or, the predominant compound(s) providing flavoring in crude extract, oil or other complex flavoring mixture, or the marker compound(s) of these complex mixtures, if the predominant compound(s) cannot be identified), a test should be conducted according to **Sections 3.3** or **3.4**, as relevant.

When a suitable analytical method to quantify the flavoring agent is not available in feed or in drinking water for animals, the applicant should adequately describe the approach/dilution process used to incorporate the flavoring agent in the feed or in drinking water for animals to ensure the uniform distribution. It is recommended to consult each jurisdiction's regulatory

agency regarding acceptable alternative approaches to demonstrate the uniform distribution of a flavoring agent in feed and drinking water for animals.

4.3 Colorant⁴

The homogeneity test for a colorant in the ingredient market formulation and in premixture should be conducted according to **Sections 3.1** and **3.2**, as appropriate.

When the intended effect of the colorant is to add or restore color to feed or drinking water for animals or is used in feed for ornamental fish and birds, a homogeneity test in feed or drinking water is normally not necessary. For a colorant to be used in feed or drinking water for animals for pigmenting tissues or animal products (e.g. eggs) of food producing animals, a homogeneity test in feed or drinking water should be conducted under the conditions of proposed use according to **Sections 3.3** or **3.4**, as appropriate.

5. SAMPLING FOR A HOMOGENEITY TEST

A proper homogeneity test should be conducted using at least 10 samples taken from one batch of intended matrix under assessment. Each sample should contain enough quantity⁵ to be representative of the batch and to carry out the necessary analyses. Samples from commercial production batch are preferred to be used in homogeneity tests. If samples from pilot or laboratory scale production are used, the mixing process using pilot or laboratory scale equipment should be comparable with the mixing process of commercial production. A justification should be provided to support the assumption that the homogeneity data obtained from the pilot or laboratory scale batch reflect the distribution of the feed ingredient in the commercial production batch.

To ensure that the samples taken are representative of the distribution of the feed ingredient in the batch under assessment, an appropriate sampling approach should be employed and provided to the regulatory agency. The following are some approaches that can

⁴ In the United States of America, the Center for Veterinary Medicine (CVM) of the U.S. Food and Drug Administration (FDA) approves the food additives used in animal food (including drinking water for animals). However, color additives, including those intended to be used in animal food, are approved by FDA's Center for Food Safety and Applied Nutrition (CFSAN). Please contact CFSAN or visit www.fda.gov for detailed information regarding data and information needed for a color additive approval.

⁵ The word "quantity" in the context of this guidance document includes mass for solids and volume or mass for liquids.

be used. These approaches are applicable to both dry and liquid forms of intended matrices including drinking water for animals, as relevant:

a. Timed sampling during the production process:

Samples of same quantity taken randomly throughout the entire course of emptying the mixer/blender or at the final production step (e.g. pelleting or extrusion process). Randomization should ensure a proper time distribution and may be accomplished by stratifying the production process time into equal length time blocks and then randomly sampling within each block. The table below shows two examples of timed sampling. The first example (Randomization 1) is an unbalanced time representation, in which 50 % of the samples are taken during the first 20 minutes of the one-hour process. While the sampling time points shown in the second example (Randomization 2) represent a proper time distribution during the entire one-hour process.

Samples	1	2	3	4	5	6	7	8	9	10
Randomization 1	3'	5'	8'	12'	20'	22'	25'	35'	45'	55'
Randomization 2	5'	12'	17'	24'	30'	34'	40'	47'	52'	58'

b. Sampling in a bulk container:

Samples of same quantity are taken at different locations and depths within the container. The locations and depths of the sampled points should be evenly distributed throughout the container. The sampling process should avoid unnecessary disturbance to the matrix in the bulk container.

c. Sampling from different containers of the same batch:

Samples of same quantity are taken from at least 10 containers randomly selected throughout the entire batch.

Sampling equipment must be suitable for taking representative samples from the intended matrix under assessment (e.g. grain probe, or other standardized particulate matter, or liquid sampling device). The sampling equipment should be properly cleaned between each sample to avoid potential carry-over from one sample to another. Samples taken from each specified location/time point should be of the same quantity. Each sample should be of enough quantity to be representative of the batch and to carry out the necessary analyses, whichever is greater. Any further mixing among samples must be avoided.

Samples must be properly labelled with, at least, the sampled intended matrix, the expected level of the feed ingredient/active substance and the origin of the sample (time or location of the samples depending on the sampling method used).

It may be acceptable to design a homogeneity test in combination with a stability test for the same intended matrix. However, the test design, sampling approach and data evaluation for either homogeneity or stability test should be appropriate for the intended purpose.

6. DATA EVALUATION AND STATISTICAL ANALYSIS

The analytical results from all samples should be presented. A CV calculation should be based on the analytical results of all the samples.

Several factors may impact the acceptability of a CV value, for example, the inclusion level of the feed ingredient in the intended matrix, analytical method uncertainty, and safety profile of the feed ingredient. A target CV value should be established before the initiation of the homogeneity test. The established target CV value should be appropriate to demonstrate the uniform distribution of the feed ingredient in the intended matrix under the conditions of proposed use.

7. DATA REPORTING

The homogeneity testing report should include a description of the test, including the sampling approach, and all analytical data. The CV should be reported based on the analytical results of all the samples.

7.1 The Description of a Homogeneity Test Should Include:

- a. Identity of the ingredient under test.

Note: Documentation (e.g. Certificates of Analyses) should be provided to demonstrate the name, batch numbers, manufacturing dates and contents of the feed ingredient under test.

- b. Analyte(s) and parameter(s) that are tested for, including the active substance, predominant substance, and marker compound, when relevant.
- c. Qualitative and quantitative compositions of each intended matrix used in the test.
- d. Proposed inclusion level of the feed ingredient in each intended matrix.
- e. Mixing procedure for each tested intended matrix.

- f. Description of the sampling approach for each tested intended matrix, including the number of samples and quantity of each sample, as well as the sampling time points during the production process, location within a bulk container or across containers.
- g. Name and address of the testing facility.

7.2 The Analytical Data Should Include:

- a. Actual test date.
- b. Individual analytical results with measurement units for each sample with a reference to the batch number.

*Note: The Certificates of Analyses should be provided. In specific cases and when requested by the regulatory agency, original analyst worksheets, spectra, chromatograms, charts, or other pertinent information may need to be submitted to support and verify reported analytical results. The CV should be calculated using the analytical results of all the samples (see **Section 6**). When providing instrument/computer printouts, explanations should be included to clarify information such as sample identification, method code, etc. It is recommended to consult each jurisdiction's regulatory agency to determine whether the original data are necessary for a specific submission.*

- c. Description of the laboratory sampling processes.
- d. Description of analytical method(s) used.

Note: If an analytical method is not a regulatory or internationally accepted method for the intended analysis, method validation information may be needed to support the use of the method in the homogeneity test.

- e. Evaluation (e.g. statistical analysis) of the data and summarized data presentation (tables, charts, etc.).

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9. ABBREVIATIONS

CV	Coefficient of Variation
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