GMP+ International

Control of residues & homogeneity of critical feed additives and veterinary medicinal products

GMP+ BA 2

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GMP+ Feed Certification scheme

Feed Safety Worldwide

gmpplus.org

History of the document

Revision no. - Date of approval	Amendment	Concerns	Final implementation date
0.0 / 06-2014	This is a new document. The content consists of the former Part B of GMP+ BA1 *Product Standards* and the former Part B of GMP+ BA4 *Sampling and* analysis. The opportunity has been taken to update a number of requirements	Entire document	01.01.2015, except sections 4.2.4 and 4.2.5, which must be implemented 1-10-2015
1.0 / 04-2017	Methods for measuring Homogeneity of dry mixtures is added Incorrect references adapted	6 5	01.07.2018
1.1 / 05-2018	Modification standard Decoquinate, due to changes in legislation	Chapter 3	01.07.2018
2.0 / 01-2019	The following is amended: - Section 5.7: The checking procedure for the process accuracy of compound feed with micro tracers is updated - at section 5.4, 5.8 and 5.9 an important note is added.	Chapter 5	01.04.2019
3.0 / 10-2021	This document is updated.	Entire document	01.01.2023

Editorial note:
All changes in this version of the document are made visible. This is how you can recognize:
- New text
- ~~Old text~~
The changes must be implemented by the participant latest at the final implementation date.

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1 INTRODUCTION

1.1 General

The GMP+ Feed Certification scheme was initiated and developed in 1992 by the Dutch feed industry in response to various more or less serious incidents involving contamination in feed materials. Although it started as a national scheme, it has developed to become an international scheme that is managed by GMP+ International in collaboration with various international stakeholders.

Even though the GMP+ Feed Certification scheme originated from a feed safety perspective, in 2013 the first feed responsibility standard has been published. For this purpose, two modules are created: GMP+ Feed Safety Assurance (focussed on feed safety) and GMP+ Feed Responsibility Assurance (focussed on responsible feed).

GMP+ Feed Safety Assurance is a complete module with standards for the assurance of feed safety in all the links of the feed chain. Demonstrable assurance of feed safety is a 'license to sell' in many countries and markets and participation in the GMP+ FSA module can facilitate this excellently. Based on needs in practice, multiple components have been integrated into the GMP+ FSA standards, such as requirements for a feed safety management system, for application of HACCP principles, for traceability, monitoring, prerequisites programmes, chain approach and the Early Warning System.

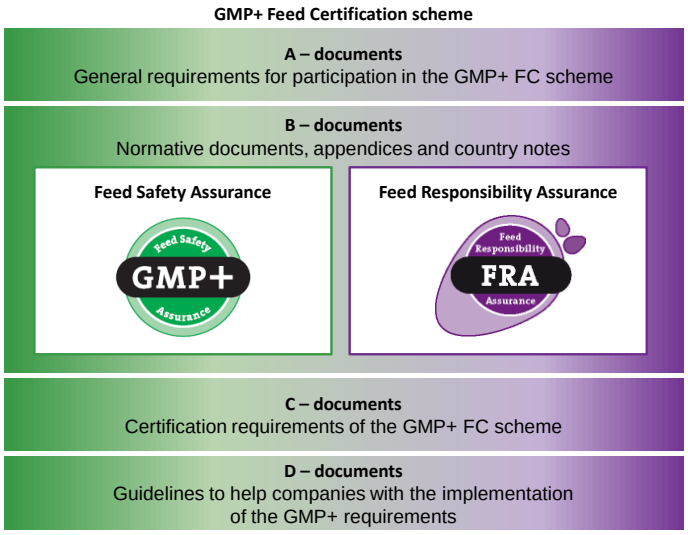
With the development of the GMP+ Feed Responsibility Assurance module, GMP+ International is responding to requests from GMP+ participants. The animal feed sector is confronted with requests to operate more responsible. This includes, for example, the sourcing of soy and fishmeal which are produced and traded with respect for humans, animals and the environment. In order to demonstrate responsible production and trade, a company can get certified for the GMP+ Feed Responsibility Assurance. GMP+ International facilitates via independent certification the demands from the market.

Together with the GMP+ partners, GMP+ International transparently lays down clear requirements in the Feed Certification scheme. Certification bodies are able to carry out GMP+ certification independently.

GMP+ International supports the GMP+ participants with useful and practical information by way of a number of guidance documents, databases, newsletters, Q&A lists and seminars.

1.2 Structure of the GMP+ Feed Certification scheme

The documents within the GMP+ Feed Certification scheme are subdivided into a number of series. The next page shows a schematic representation of the content of the GMP+ Feed Certification scheme:



All these documents are available via the website of GMP+ International (www.gmpplus.org).

This document is referred to as appendix GMP+ BA2 *Control of residues* and is part of the GMP+ FSA scheme.

1.3 Scope and application of this document

~~In this appendix specific requirements regarding the control of residues of a number of veterinary medical products and feed additives are laid down.~~

- ~~Section 2 gives a number of general requirements~~
- ~~In Section 3 limits for residues of a number of veterinary medical products and feed additives are laid down. These limits may not be exceeded.~~

> ~~*Explanation*~~
> ~~*Veterinary medical products and feed additives are critical when in milk, meat or eggs their residues can be present, but unwanted / undesirable. The level of these residues in feed must be controlled and must not exceed certain limits.*~~

- ~~Section 4 gives additional requirements for the control of these critical veterinary medical products and feed additives. There are several options given.~~
- ~~In section 5 of this appendix a number of protocols are laid down to measure the carry-over of a feed production installation. Where measuring the carry-over percentage of installations, facilities and equipment, one of these protocols must be applied. However, when due to national legislation application of specific methods for measuring the carry-over is required, these methods and their results are also acceptable.~~

This Appendix contains requirements for a GMP+ certified company that processes critical feed additives and/or veterinary medicinal products, regarding

- the control of residues
- homogeneity.

~~**2 Background information**~~

~~**3 Limits for critical residues**~~

~~**4 Additional requirements for the control of residues**~~

~~**5 METHODS FOR MEASURING CARRY-OVER**~~

~~**6 METHODS FOR MEASURING HOMOGENEITY OF DRY MIXTURES**~~

The chapters mentioned above (Ch. 2-6) have been replaced by the following new chapters and, for a better readability, it has been decided to delete the old chapters.
All previous versions can be consulted on the website.

2 CONTROL OF RESIDUES

2.1 Application of HACCP principles

- A GMP+ certified company must define control measures to ensure that residues of critical feed additives and veterinary medicinal products do not exceed the limits laid down in Annex 2.

  Note: Possible and often used control measures are:
  - Use of dedicated production and transport lines within a location
  - Flushing/sequencing: see chapter 2.2
  - Physical clean-out
  - A combination of above-mentioned control measure(s).

- Any measure or combination of measures to control the residues of critical feed additives / veterinary medicinal products must be validated.
  - Validation of control measures which are applied on non-dedicated production/transport lines, must involve analysing at least 2 representative samples of feed for which residue limits are laid down in Annex 2.
  - When using dedicated production/transport lines, the company must demonstrate and document that residue limits, laid down in Annex 2, are not exceeded.

- The ongoing effectiveness of the control measures must be monitored at least quarterly. This is done by analysing, in a representative sample, the residue level of the processed critical feed additive or veterinary medicinal product.
  If the company processes several types of critical feed additives and/or veterinary medicinal products, these should be analysed in turn.

Guidance
Suppose you are processing 6 different coccidiostats. You include all 6 of these coccidiostats in the analysis schedule: in the 1st quarter you analyse for residues of coccidiostat A, in the second quarter for residues of coccidiostat B, etc. After 6 quarters (1.5 years) you have analysed all coccidiostats on residues and start again with an analysis for residues of coccidiostat A.

- Analysis must be carried out by a laboratory that is approved as such (see for this GMP+ BA10 *Minimum Requirements for Purchasing*).

2.2 Additional requirements for flushing

A commonly used control measure is to ‘clean’ the production installation by flushing it with feed, right after the production of a feed in which a critical feed additive or a veterinary medicinal product is processed.

The following conditions apply:

- Flushing must be done with a defined, validated volume of a feed. This flushing batch size matches the batch size used in normal daily production, unless the company demonstrates, based on site-specific research, that a smaller batch size provides sufficient cleaning. Validation must include analysis of at least 2 representative samples.

- A feed material, used for flushing, must be carefully handled and processed afterwards, so that all legal regulations are met and feed safety issues are avoided. This must be supported by a hazard analysis.

- When placed on the market, the feed used for flushing, must comply with applicable legislation. In any case, the levels of critical feed additives/veterinary medicinal products (Annex 2) must not be exceeded.

- In case the installation is flushed via a calculated production sequence based on measured carry-over percentage, then the periodical verification of the effectiveness (as required in chapter 2.1) may be reduced by 50%, provided that the method used to measure the carry-over complies with the criteria in Annex 1.

- When choosing the flushing method, the company takes into account national feed legislation including the interpretation by the competent authorities. Any deviation from the above conditions must be justified and documented.

Guidance
Flushing via a calculated production sequence based on measured carry-over percentage is preferable

3 HOMOGENEITY

Every mixer, in which dry mixtures with critical feed additives or veterinary medicinal products are produced, must be tested to demonstrate its effectiveness regarding homogeneity. The method used to measure the homogeneity must comply with the criteria in Annex 1.

Depending on the method used, the results must be interpreted based on the limits in the next tables:

Determination of homogeneity by means of direct methods

Probability p	**Assessment**
p ≤ 1%	Insufficient
1% < p < 5%	Probably significant deviation. No unambiguous statement can be made. The test must be repeated.
P ≥ 5%	Good homogeneity

Determination of homogeneity by means of indirect methods

Coefficient of variation CV	**Assessment**
CV ≤ 8%	Good homogeneity
8% < CV < 12%	Acceptable homogeneity
CV ≥ 12%	Insufficient

If the homogeneity of the mixture is assessed as insufficient, the GMP+ certified company must carry out a root cause analysis, take corrective measures and perform a new homogeneity test in order to verify that the measures taken are effective in achieving a sufficient homogeneity.

Annex 1: Criteria for measurement of carry-over and homogeneity

The table below gives minimum criteria for measuring carry-over[1] and homogeneity. There may be some overlap between methods to measure carry over and homogeneity. This is why a lot of companies combine the measurement of carry over and homogeneity. Note that combining of these both measurements is not an obligation.

In some countries, special requirements to measure the carry-over level and homogeneity are laid down in legislation. Those measurement methods are accepted.

Explanation table below:
In some cases there are different criteria mentioned (e.g. Measurement method), but in case the criteria is the same for both carry-over and homogeneity, there is no separation in the table (e.g. Tracer).

	Homogeneity	Carry-over
Measurement method *See guidance below 1, 2 and 3*	• The measurement of homogeneity is statistically determined, by making use of direct or indirect methods. ○ Direct methods are based on the counting of particles. Application of these methods lead to analysis results, which are analysed as Poisson distributions. Homogeneity is expressed in terms of probability (p). ○ Indirect methods are based on the determination of concentration of a substance. Application of these methods lead to analysis results, which are considered	• The test must measure the carry-over level of all relevant parts of the whole production process from intake of critical feed additives and / or veterinary medicinal products up to packaging of the feed or loading for delivery. • The test must be able to measure at least a carry-over level of 1% for compound feed, and 0.5% for premixtures.

[1] Note that the GMP+ standard does not require certified companies to measure the carry-over level (chapter 2.2) of a production installation. But if measured, the method used must meet the criteria in this table.

	Homogeneity	Carry-over
	as being normal distributions. Homogeneity is given by the coefficient of variation (CV).	
Frequency	The carry-over and homogeneity must be measured at first use of an installation and re-measured after significant modification of the installation.	
	Further, at least every 4 years	Further, at least every 2 years.
Tracer *See guidance below (indent 1)*	• Is suitable and detectable with sufficient accuracy at low levels and stable during the production steps • Only one ingredient (the tracer itself) must contribute to the concentration of the tracer in the test batches unless the contribution from other ingredients to the concentration of the tracer is known and is limited • When the tracers are particles they must be visual detectable and preferably coloured Note: Macro elements (e.g. Ca, Na) are not allowed to measure carry-over and homogeneity of mixtures containing critical feed additives / veterinary medicinal products**.**	
Sampling and analysing	• Each sample must contain enough quantity to carry out the necessary analyses (incl. re-testing). • The number of samples to measure carry-over and homogeneity with the desired accuracy must fit the method and the batch size. The minimum number of samples is 10. • Samples must be properly labelled. • Analysis must be carried out by a laboratory that is approved as such (see GMP+ BA10 *Minimum Requirements for Purchasing)*	
	• Sampling must take place in the mixer / blender (at predefined spots and evenly spread across the mixer) or at regular intervals while the mixer / blender is being emptied .	• For each batch, the samples must represent the whole batch and are taken with equally intervals of time at the end of the production line.

	Homogeneity	Carry-over
Process parameters	• Filling rate, mixing time, etc. must meet normal production circumstances.	• The test batches (tracer batch and carry-over batch) must be manufactured using the facility's normal feed manufacturing practices, e.g.: batch size, routing and sequence of dosing ingredients.
Reporting	• The performances and the results of the measurements must be retained as documented information.	

Guidance
1. Use as much as possible one type of tracer/method to make better comparisons with previous tests.
2. The tracer must follow the same route as the critical feed additives and / or veterinary medicinal product through the installation.
3. GMP+ Support documents contain more detailed descriptions of methods for measuring carry-over and homogeneity (see S 9.14 *Methods for measuring carry-over & homogeneity of critical feed additives and veterinary medicinal products)*.

Annex 2: Residue limits

The next table below shows the residue limits for critical feed additives / veterinary medicinal products.

Critical Feed additives (Coccidio-stats)	Feed	Maximum content in mg/kg (ppm) relative to a feed with a mois-ture content of 12 %
Lasalocid A so-dium	Feed materials	1,25
	Compound feed for: • dogs, calves, rabbits, equine species, dairy animals, laying birds, turkeys (> 16 weeks) and chickens reared for laying (> 16 weeks) • chickens for fattening, chickens reared for laying (< 16 weeks) and turkeys (<16 weeks) for the period before slaughter in which the use of Lasalocid A sodium is prohibited (withdrawal feed) • pheasants, guinea fowl, quails and partridges (except laying birds) for the period before slaughter in which the use of Lasalocid A sodium is prohibited (withdrawal feed) • other animal species	1,25 1,25 1,25 3,75
	Premixtures for use in feed in which the use of Lasalocid A so-dium is not authorised.	([1])
Narasin	Feed materials	0,7
	Compound feed for: • turkeys, rabbits, equine species, laying birds and chickens reared for laying (> 16 weeks) • other animal species	0,7 2,1
	Premixtures for use in feed in which the use of Narasin is not au-thorised.	([1])
Salinomycin sodium	Feed materials	0,7
	Compound feed for: • equine species, turkeys, laying birds and chickens reared for laying (> 12 weeks) • chickens for fattening, chickens reared for laying (< 12 weeks) and rabbits for fattening for the period before slaughter in which the use of Salinomycin sodium is prohibited (withdrawal feed) • other animal species	0,7 0,7 2,1
	Premixtures for use in feed in which the use of Salinomycin so-dium is not authorised.	([1])
Monensin so-dium	Feed materials	1,25
	Compound feed for: • equine species, dogs, small ruminants (sheep and goat), ducks, bovine, dairy animals, laying birds, chickens reared for laying (> 16 weeks) and turkeys (> 16 weeks) • chickens for fattening, chickens reared for laying (< 16 weeks) and turkeys (< 16 weeks) for the period before slaughter in	1,25 1,25

Critical Feed additives (Coccidio-stats)	Feed	Maximum content in mg/kg (ppm) relative to a feed with a mois-ture content of 12 %
	which the use of Monensin sodium is prohibited (withdrawal feed) • other animal species	 3,75
	Premixtures for use in feed in which the use of Monensin sodium is not authorised.	([1])
Semduramicin sodium	Feed materials	0,25
	Compound feed for: • laying birds and chickens reared for laying (> 16 weeks) • chickens for fattening for the period before slaughter in which the use of Semduramicin sodium is prohibited (withdrawal feed) • other animal species	 0,25 0,25 0,75
	Premixtures for use in feed in which the use of Semduramicin so-dium is not authorised.	([1])
Maduramicin ammonium al-pha	Feed materials	0,05
	Compound feed for: • equine species, rabbits, turkeys (> 16 weeks), laying birds and chickens reared for laying (> 16 weeks) • chickens for fattening and turkeys (< 16 weeks) for the period before slaughter in which the use of Maduramicin ammonium alpha is prohibited (withdrawal feed) • other animal species	 0,05 0,05 0,15
	Premixtures for use in feed in which the use of Maduramicin ammonium alpha is not authorised.	([1])
Robenidine hydro-chloride	Feed materials	0,7
	Compound feed for: • laying birds and chickens reared for laying (> 16 weeks) • chickens for fattening, rabbits for fattening and breeding and turkeys for the period before slaughter in which the use of Robenidine hydrochloride is prohibited (withdrawal feed) • other animal species	 0,7 0,7 2,1
	Premixtures for use in feed in which the use of Robenidine hydro-chloride is not authorised.	([1])
Decoquinate	Feed materials	0,4
	Compound feed for: • laying birds and chickens reared for laying (> 16 weeks) • other animal species	 0,4 1,2
	Premixtures for use in feed in which the use of Decoquinate is not authorised	([1])
Halofuginone hydro-bromide	Feed materials	0,03
	Compound feed for: • laying birds, chickens reared for laying and turkeys (> 12 weeks) • chickens for fattening and turkeys (< 12 weeks) for the period before slaughter in which the use of Halofuginone hydro bro-mide is prohibited (withdrawal feed) • other animal species	 0,03 0,03 0,09

Critical Feed additives (Coccidio-stats)	Feed	Maximum content in mg/kg (ppm) relative to a feed with a mois-ture content of 12 %
	Premixtures for use in feed in which the use of Halofuginone hy-dro bromide is not authorised.	(1)
Nicarbazin	Feed materials	1,25
	Compound feed for: • equine species, laying birds and chickens reared for laying (> 16 weeks) • other animal species	1,25 3,75
	Premixtures for use in feed in which the use of Nicarbazin (in combination with Narasin) is not authorised.	(1)
Diclazuril	Feed materials	0,01
	Compound feed for: • laying birds, chickens reared for laying (> 16 weeks) • rabbits for fattening and breeding for the period before slaugh-ter in which the use of Diclazuril is prohibited (withdrawal feed). • other animal species other than chickens reared for laying (< 16 weeks), chickens for fattening, guinea fowl and turkeys for fattening.	0,01 0,01 0,03
	Premixtures for use in feed in which the use of Diclazuril is not au-thorised.	(1)
For other criti-cal feed addi-tives (3)	Feed	Max. Percentage (%)
	All non-target feed for food producing animals	1% of the max. content, which is approved to mix in feed. (2)
	All other non-target feed	3% of the max. content, which is approved to mix in feed (2)
Veterinary me-dicinal prod-ucts (4)	Feed	Max. Percentage (%)
	All non-target feed	1 % of the max. content which is prescribed to mix in feed (2)

(1) The maximum level of the feed additive/veterinary medicinal product in the premixture must not result in a level of that feed additive/veterinary medicinal product higher than 50 % of the maximum levels established in the feed when the instructions for use of the premixture are followed.

(2) Certified companies are allowed to deviate from this maximum level if national legislation allows this and when the feed is placed on the local market. If national legislation requires stricter maximum limits, this must also be taken into account.

(3) 'Other critical feed additives' are products:

- *which are deliberately added to the feed with the intention to influence performance, production or health of the animal, and*
- *which can be found in the animal products (meat, milk or egg), and can be harmful when consumed by humans, and*
- *for which subsequently a withdrawal time has been defined.*

(4) Examples: antibiotics, anthelmintics.

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