Technical Specifications

TS1.11 - Control of residues & homogeneity

Version EN: 1 January 2022

GMP+ International

gmpplus.org

Index

1. Scope and application of this document

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

- the control of residues
- homogeneity.

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 *Appendix 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 *Appendix 2*.
- When using dedicated production/transport lines, the company must demonstrate and document that residue limits, laid down in *Appendix 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 must be analysed in turn.

Helpful tip:
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 TS1.2 *Purchase*).

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:

a. 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.

b. 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.
c. 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 (*Appendix 2*) must not be exceeded.
d. 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 *Appendix 1*.
e. 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.

Helpful tip:

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 *Appendix 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.

Appendix 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 helpful tip 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 as being normal distributions. Homogeneity is given by the coefficient of variation (CV).	• 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.
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.

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
Tracer *See helpful tip 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 for this TS1.2 *Purchase*)	
	• Sampling must take place in the mixer / blender (at pre-defined 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.
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.	

Helpful tip:
Use as much as possible one type of tracer/method to make better comparisons with previous tests.

Helpful tip:
The tracer must follow the same route as the critical feed additives and / or veterinary medicinal product through the installation.

Helpful tip:

GMP+ Support documents contain more detailed descriptions of methods for measuring carry-over and homogeneity (see S9.14 *Methods for measuring carry-over & homogeneity of critical feed additives and veterinary medicinal products).*

Appendix 2: Residue limits

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

Critical Feed additives (Coccidiostats)	**Feed**	**Maximum content in mg/kg (ppm) relative to a feed with a moisture content of 12 %**
Lasalocid A sodium	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 sodium is not authorised.	([2])
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 authorised.	([2])
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 forbidden (withdrawal feed) • other animal species	0,7 0,7 2,1
	Premixtures for use in feed in which the use of Salinomycin sodium is not authorised.	([2])

Critical Feed additives (Coccidiostats)	**Feed**	**Maximum content in mg/kg (ppm) relative to a feed with a moisture content of 12 %**
Monensin sodium	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 which the use of Monensin sodium is prohibited (withdrawal feed) • other animal species	1,25 1,25 3,75
	Premixtures for use in feed in which the use of Monensin sodium is not authorised.	([2])
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 forbidden (withdrawal feed) • other animal species	0,25 0,25 0,75
	Premixtures for use in feed in which the use of Semduramicin sodium is not authorised.	([2])
Maduramicin ammonium alpha	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 forbidden (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.	([2])
Robenidine hydro-chloride	Feed materials	0,7
	Compound feed for: • laying birds and chickens reared for laying (> 16 weeks)	0,7 0,7

Critical Feed additives (Coccidiostats)	Feed	Maximum content in mg/kg (ppm) relative to a feed with a moisture content of 12 %
	• chickens for fattening, rabbits for fattening and breeding and turkeys for the period before slaughter in which the use of Robenidine hydrochloride is forbiddden (withdrawal feed) • other animal species	2,1
	Premixtures for use in feed in which the use of Robenidine hydrochloride is not authorised.	([2])
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	([2])
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 bromide is forbidden (withdrawal feed) • other animal species	0,03 0,03 0,09
	Premixtures for use in feed in which the use of Halofuginone hydro bromide is not authorised.	([2])
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.	([2])
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 slaughter in which the use of Diclazuril is forbidden (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 authorised.	([2])

Critical Feed additives (Coccidiostats)	**Feed**	**Maximum content in mg/kg (ppm) relative to a feed with a moisture content of 12 %**
For other critical feed additives ([3])	Feed	Max. Percentage (%)
	All non-target feed for food producing animals	1% of the max. content, which is approved to mix in feed. ([4])
	All other non-target feed	3% of the max. content, which is approved to mix in feed ([4])
Veterinary medicinal products ([5])	Feed	Max. Percentage (%)
	All non-target feed	1 % of the max. content which is prescribed to mix in feed ([4])

2. 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.

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. 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.

5. Examples: antibiotics, anthelmintic

Feed Support Products

That was a lot of information to digest and one might ask, what is the next step? Luckily we can offer support for the GMP+ Community when doing this. We provide support by means of various tools and guidances but as each company has a shared responsibility to feed safety, and therefor tailor-made solutions cannot be offered. However, we do help by explaining requirements and provide background information about the requirements.

We have developed various supporting materials for the GMP+ Community. These include various tools, ranging from Frequently Asked Questions (FAQ) lists to webinars and events.

Supporting materials related to this document (Guidelines and FAQ's)

We have made documents available which give guidance to the GMP+ requirements as laid down in the module GMP+ FSA and GMP+ FRA. These documents give examples, answers to frequently asked questions or background information.

We enable every company in the feed chain to take responsibility for safe and sustainable feed.

GMP+ International
Braillelaan 9
2289 CL Rijswijk
The Netherlands
t. +31 (0)70 – 307 41 20 (Office)
+31 (0)70 – 307 41 44 (Help Desk)
e. info@gmpplus.org