GMP+ International

Control of residues

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

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.

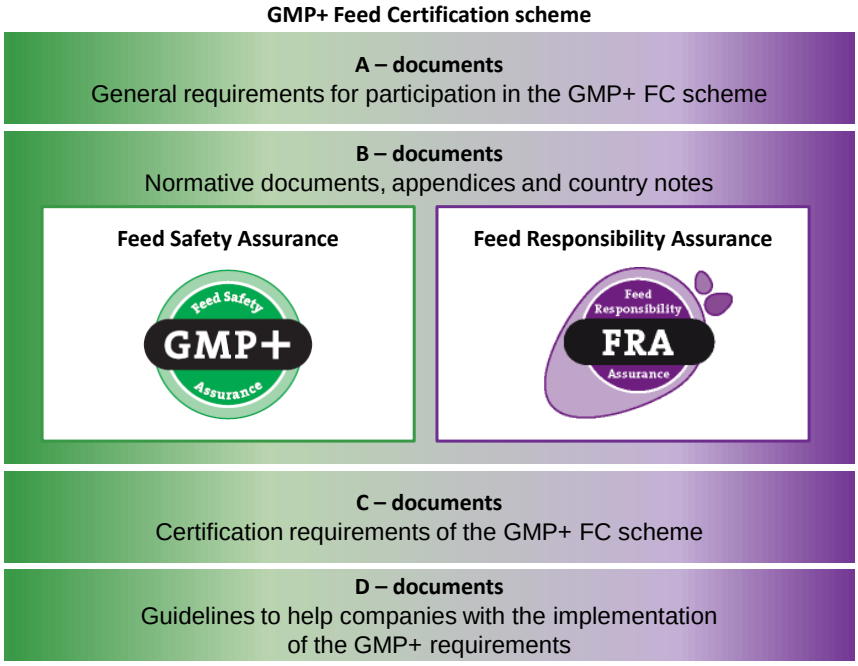
With the development of the GMP+ Feed Responsibility Assurance module, GMP+ International is responding to requests from GMP+ participants. The animal feed sector is confronted with requests to operate more responsible. This includes, for example, the sourcing of soy and fishmeal which are produced and 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

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.

2 Background information

1. Correct use of feed additives and veterinary medical products when producing (compound) feed or premixtures contributes to feed and food safety. Therefore, GMP+ standards include requirements to control the use of veterinary medical products and feed additives, including their residues. The participant must ensure that
   a. the correct feed additives and veterinary medical products is dosed in the right amount into the right feed.
   b. (residues of) these feed additives and veterinary medical products are not present in all other feed or do at least not exceed maximum limits (the so-called limits) in all those other feed.

2. The residue limits in this appendix are mainly based on EU legislation. These residue limits are adopted into the GMP+ FSA module. Any company, participating in the GMP+ FC scheme, whether located inside or outside Europe, must – if applicable -comply with these residue limits.

   In general, the residue limit of a certain feed additive or is a percentage of the maximum content, which is allowed to mix into feed. In the EU Feed legislation residue limits are laid down, based on the factors in the next table

Feed additive/Veterinary medical product	**Max. percentage (%)**	**Remark**
Coccidiostats	1	For critical feed
	3	For other feed
Antibiotics	2.5	

   These limits have been specified in the table in section 3. Also, for a number of other substances residue limits have been specified in this table, mainly calculated with a ‘max 2.5%-factor’.

3. In EU legislation only residue limits are specified for feed additives that are approved in the EU for application in feed. In other parts of the world, also other substances (specific coccidiostats ‘veterinary medical products’- or products like Olaquindox and Carbadox) are approved to use as veterinary medical products or feed additives. The residue limits for these products must be calculated based on the above given percentages. In the table in section 3 these products should be classified under ’Other substances for which a withdrawal time has been established’.

   Guidance
   ‘Other substances for which a withdrawal time has been established’ 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 man, and*
   - *for which subsequently a withdrawal time has been defined.*

4. The applicable legal requirements for the use of the feed additives and veterinary medical products must be met, including dosing and labelling. When legislation requires respecting other limits, also these requirement must be met.

Guidance
Note that the GMP+ requirements are mainly based on EU legislation. However, this does – for instance - not mean that a company located outside Europe, is not allowed to produce or process a feed additive that is not approved in the EU. Such an additive may be produced or processed under GMP+ conditions and the system for assuring this production can be GMP+ certified. However, such a feed additive cannot be used as a feed additive in feeds for EU-market. A GMP+ certificate is not a license to export to Europe.

3 Limits for critical residues

The next table below shows the limits for critical residues from a number of feed additives / veterinary medical products.

Additives	Products intended for animal 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) - other animal species	1,25 1,25 3,75
	- 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),	1,25
	Premixtures for use in feed in which the use of Lasalocid sodium 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 authorised.	(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 sodium is not authorised.	(1)
Monensin sodium	Feed materials	1,25

Additives	Products intended for animal feed	Maximum content in mg/kg (ppm) relative to a feed with a moisture content of 12 %
	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.	(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 sodium is not authorised.	(1)
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 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

Additives	Products intended for animal feed	Maximum content in mg/kg (ppm) relative to a feed with a moisture content of 12 %
	Premixtures for use in feed in which the use of Robenidine hydrochloride is not authorised.	(1)
Decoquinate	Feed materials	0,4
	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 Decoquinate is prohibited (withdrawal feed)~~ - other animal species	0,4 ~~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 bromide is prohibited (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	(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 slaughter 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 authorised.	(1)

Additives	Products intended for animal feed	Maximum content in mg/kg (ppm) relative to a feed with a moisture content of 12 %
	Note: • Chickens for fattening: feed given to these chickens from 5 days before slaughter • Turkeys for fattening: feed given to these turkeys from 5 days before slaughter • Pigs: feed given to pigs from 28 days before slaughter	
For other coccidiostats	For all feed	1% of the max. content, which is approved to mix in a feed.
Veterinary medical products	**Products intended for animal feed**	**Maximum content in mg/kg (ppm) relative to a feed with a moisture content of 12 %**
Sulfadiazine sodium	Compound feed for: - Laying birds - Chickens for fattening and Turkeys for fattening - Pigs - Dairy animals	 5 8 1 1
Sulfamethoxazol	Compound feed for - Laying birds - Chickens for fattening and Turkeys for fattening - Pigs - Dairy animals	 5 8 1 1
Doxycycline	Compound feed for - Laying birds - Chickens for fattening and Turkeys for fattening - Pigs - Dairy animals	 8 8 10 1 batch[2]
Oxytetracycline	Compound feed for - Laying birds - Chickens for fattening and Turkeys for fattening - Pigs - Dairy animals	 1 10 10 1 batch[2]
Ivermectine	Compound feed for - Laying birds - Chickens for fattening and Turkeys for fattening - Pigs - Dairy animals	 0,1 0,1 0,1 1 batch[2]
Tiamuline	Compound feed for - Laying birds - Chickens for fattening and Turkeys for fattening - Pigs - Dairy animals	 1 8 10 1 batch[2]

Veterinary medical products	Products intended for animal feed	Maximum content in mg/kg (ppm) relative to a feed with a moisture content of 12 %
Tilmicosine	Compound feed for - Laying birds - Chickens for fattening and Turkeys for fattening - Pigs - Dairy animals	 1 4 10 1 batch[2]
Trimethoprim	Compound feed for - Laying birds - Chickens for fattening and Turkeys for fattening - Pigs - Dairy animals	Linked to Sulfadiazine and therefore sufficiently guaranteed
Other feed additives/ Veterinary medical products	**Products intended for animal feed**	**Maximum content in mg/kg (ppm) relative to a feed with a moisture content of 12 %**
Other substances, for which a withdrawal time has been established[3]	All other feed for animals that produce animal products like - Laying hens - Milk producing cows, goat, sheep, etc. - Slaughter chickens and fattening turkeys (feed give from 5 days before slaughter) - Pigs (feed given from 28 days before slaughter)	1

(1) The maximum level of the substance in the premixture is the concentration which shall not result in a level of the substance higher than 50 % of the maximum levels established in the feed when the instructions for use of the premixture are followed.

(2) Dairy cow feed may not immediately be produced on a production line which has just produced with these additives/products.

(3) Examples: Flubendazol, Carbadox, Olaquindox.

4 Additional requirements for the control of residues

4.1 General / installation

A company can apply several control measures to assure that residues of critical feed additives and veterinary medical products are not exceeding the limits, laid down in the table in section 3.

Guidance
Think of:

- *Not using any feed additive or with a residue limit at all.*
- *Separation between locations where feed additives/ medicines are used, and where they are not used.*
- *Separation between production equipment and internal transport facilities (with and without critical feed additives/veterinary medical products) within a location.*
- *Choose less critical feed additives or veterinary medical products*
- *Transport of the first 50-100 kg of produced feed (after medicated feed) to the rework bin.*
- *Using specific equipment (internal transport, mixer, filter.*
- *Proper maintenance and cleaning of the equipment.*
- *Dosing veterinary medical products in the mixer or bulk blending equipment.*
- *Use of a fixed dosage sequence for micro components.*
- *Use of short ways for transport / use proper idle times.*
- *Avoiding of places where products can stay behind.*
- *Applications of a strict production sequence/flushing. See for this section 4.2.*

In all the GMP+ standards is laid down that control measures must be validated and their effectiveness must be verified with an appropriate frequency ('HACCP principles'). This includes the control measures for controlling residues of veterinary medical products / additives.

When using a specific production sequence for controlling the residue limits, specific validation & verification is required. See for this section 4.2.4.

Guidance
Validation: Must be applied in accordance with the common HACCP principles. The applicant must be sure that application of a certain control measure gives the expected result (= no residues or at least below the limits). Results of analytical research is very helpful here. After each essential change, control measures must be reconsidered and – if necessary - updated and validated.

Verification: From time to time must be checked if the applied control measure is still giving the expected result (= no residues or below the limits).

4.2 Control of residues via production sequence

4.2.1 General

A very common method used for controlling residue levels is to flush the production installation after a veterinary medical product or a feed additive is used, thus 'cleaning' an installation.
When using this method, a strict production sequence must be calculated and applied, with enough flushing batches to assure that residue levels are not exceeded.

If feed is used for flushing after a medicated feed or feed with a coccidiostat is produced, it must be assured that residue level of the veterinary medical products or the feed additives in this feed does not exceed the limits.

If a feed material is used for flushing, it must be used or processed with great care afterwards. A risk analysis must proof the correct use of this feed material. This feed material might be used in a feed with the same coccidiostat or antibiotic. It can also be disposed of as waste.

The calculation, which is based on the degree of carry-over of a production installation, results in expected levels (calculated) of residues of critical feed additives and veterinary medical products in successive batches, after the batch in which a company has used a critical feed additive or veterinary medical product.

Note:
The maximum level of the feed additive/veterinary medical product in the premixture is the concentration which shall not result in a level of this feed additive/ higher than 50 % of the maximum levels established in the feed when the instructions for use of the premixture are followed.

Guidance
For example: Max. residue limit of a feed additive for feed is 1 ppm. Premixture may contribute max. 0,5 ppm in the feed (50%). When premixture must be mixed in the feed with 5%, according to the instructions, the max. residue limit for the premixture is 10 ppm.

Also feed additives like copper and zinc have max. limits which may not be exceeded. See for this GMP+ BA1. Make sure that these limits are not exceeded.

4.2.2 Carry-over percentage of installation

4.2.2.1 General

A testing procedure laid down in section 5 of this appendix must be used for measuring the carry-over percentage of an installation. All production, processing and transport lines in a facility, which can contribute to the carry-over, must be tested. See for more details section 5.

4.2.2.2 Frequency

The minimum frequency of measuring the carry-over in production and transport lines depends on the (feed and premixtures with) feed additives and veterinary medical products which the applicant processes and whether he processes feed for which a residue limit has been established.

If the participant processes or transports (feed containing) products for which a specific residue limit has been laid down in the table in section 3, the percentage of carry-over must be known for the lines on which these products are processed, produces or transported. If the participant has such production lines, he must measure carry-over at least once per two years.

When processing or transporting any other product, which may give residues in animal products, the participant must measure the carry-over at least once.

The carry-over must be re-measured in the event of major changes to the installation.

4.2.3 Safety factor

The actual processing properties of a critical feed additive or veterinary medical product may be different from the tracers that are used during the measuring of the carry-over percentage with one of the methods that are laid down in section 5.

To achieve more guarantees that the real residue levels do not exceed the calculated (expected) residue levels, a company may use in the calculation of the production sequence a so-called safety factor. When using the safety factor in the calculation, a company may lower the verification frequency. See for this section 4.2.4.

The default safety factor to be used is “3” . However, in the tables in section 4.2.5 for a number of critical feed additives and veterinary medical products, other safety factors are laid down.

Guidance
These safety factors are determined based on a so-called relative wall adhesion factor, measured with a test specially developed for this purpose. If a company wants to use this test for establishing the specific wall adhesion factor, GMP+ International can be contacted.

4.2.4 Validation and periodically verification (‘monitoring).

4.2.4.1 Validation

Any calculated production sequence must be properly validated to show effectiveness in controlling residue levels. At least 2 samples must be taken and analysed.

When the degree of carry-over has been re-measured and the production sequence has been recalculated, a new validation must be carried out

4.2.4.2 Verification

To prove ongoing effectiveness of the used production sequence, the company has to monitor by means of analysing the residue levels in relevant feeds:

a) When not using the safety factor in the calculation of the production sequence: 4 samples per year
b) When using the safety factor in the calculation of the production sequence: 2 samples per year

Guidance
The company has a choice here. If the safety factor is used, the minimum monitoring frequency per year is lower.

Verification must be carried out by means of analysing the residue levels of the specific veterinary medical product or feed additive. When more veterinary medical products or feed additives are used in the production, the one with the highest safety factor should be analysed as part of the verification.

Analysis must be carried by a laboratory that is approved as such (See for this GMP+ BA10). The detection limit of the method used must be appropriate to decide if the established system of production sequence is sufficient.

4.2.5 Additional information about the safety factor

Table 1: Additional information about the safety factor for some coccidiostats and histomonostats, which have been tested wit he so-called wall-adhesion test.

Name	Producer	Safety factor	
		Pigs	Other
Compound of Narasin and Nicarbazin			
Maxiban G 160 premix	Eli Lilly	3	1
Lasalocid sodium			
Avatec 15% CC	Roche	1	1
Robenidine-hydrochloride			
Cycostat 66G	Roche	1	1
Monensin-sodium			
Elancoban G200 premix	Eli Lilly	1	1
Coxidin (5 1 701)	Huvepharma	1	1
Narasin			
Monteban G100 premix	Eli Lilly	1	1
Halofuginone-hydro bromine (764)			
Stenorol	Huvepharma	1	1
Diclazuril			
Clinacox 0,5 % Premix	Janssen Pharmaceutica nv	2	2
Salinomycin-sodium			
Sacox 120 microGranulate	Huvepharma	1	1
Kokcisan 12%	KRKA	1	1

Table 2: Additional information about the safety factor for some medicated premixes which have been tested wit he so-called wall-adhesion test.

Name	Producer/importer	Safety factor	
		Pigs	Other
Doxycyclinehyclaat/broomhexine hydrochloride			
Feedmix Doxy-B	Dopharma Research B.V.	2,5	2,5
Pulmodox 5% Premix	Virbac Laboratories	2,5	2,5
Doxyprex	Industrial Veterinaria S. A.	2,5	2,5
Sulfadiazinenatrium/Trimethoprim			
Feedmix Trim/sul 80/420	Aesculaap BV	3	3
Trimethosulf premix	Eurovet Animal Health B.V.	3	2
Feedmix sulfatrim	Dopharma Research B.V.	3	3
Sulfamethoxazol/Trimethoprim			
Feedmix TS	Dopharma Research B.V.	3	3
Vetmulin 10% premix for medicated feeds	Huvepharma N.V.	1	1

Name	Producer/importer	Safety factor	
		Pigs	Other
Tilmicosinefosfaat			
Tilmovet 10%, premix for medicated feed for pigs	Huvepharma N.V.	1	1
Tilmovet 4%	Huvepharma N.V.	1	1
Tilmovet 20%, premix for medicated feeds for pigs	Huvepharma N.V.	1	1
Tylosinefosfaat			
Pharmasin 20 mg/g premix	Huvepharma N.V.	1	1
Pharmasin 100mg/g premix for medicated feeds for pigs, slaughter chickens and chickens reared for laying	Huvepharma N.V.	1	1
Pharmasin 250mg/g premix for medicated feeds pigs, slaughter chickens and chickens reared for laying	Huvepharma N.V.	1	1
Flubendazol (different mixes)		3	3
Ivermectine (different mixers)		3	3

5 METHODS FOR MEASURING CARRY-OVER

5.1 Introduction

To measure the carry-over, the participant must make use of the protocols, which are laid down in this part of the appendix.

The report on the carry-over inspection must comply with further conditions. See below for a description of the methods. (see chapter 2, section: Inspection report)

N.B.
It is permissible for companies to deviate from the method laid down as long as the principle is not affected and it can be demonstrated that equivalent results will be obtained.

In some countries, in legislation special requirements to measure the carry-over are laid down. The results of these measurements are accepted to demonstrate compliance with the GMP+ requirements.

5.2 General basic principles with respect to the measurement of carry-over

When measuring the carry-over of additives in an installation there must be a prior examination using a block diagram (graphic reproduction of e.g. a factory) and the actual situation in the factory of which parts of the factory may be relevant for carry-over.

A basic principle in determining carry-over in a company is that the degree of carry-over as a result of return flows is known and is controlled.

Carry-over points

Carry-over in a (compound feed) factory may occur in the following processes.

1. **The filling of premix silos**
   The filling of the premix silos may be the cause of carry-over. The block diagram can be used to find out whether there are reasons to suppose that carry-over occurs here. Critical points are common transport systems, chutes, separation systems and filters.

   In mechanical transports such as mass transports, elevators and screw conveyors, carry-over always occurs and it is sensible to measure this carry-over. Also, sufficiently long idle times (10 minutes) should be taken into account.

   For the pneumatic filling method with separate filters for each silo, no account needs to be taken of carry-over. If there is a common filter then the filter must, for at least 10 minutes after unloading, be knocked on the same silo as that in which the filling took place.

   There should be an instruction for the dumping sequence so that undesired mixing does not take place.

   In this situation it must be certain that unacceptable residue levels no longer occur.

2. **Dosage, grinding and mixing line**
   The greatest amount of carry-over of additives and veterinary medical products occurs in the dosage process (addition of additives or veterinary medical products) / (possibly grinding) / mixing / transport and storage of the product in meal form in a finished product cell or a pressed meal cell.

   The place where premixes are added should be as close to the mixer as possible. It is important that the measured substance is added at the same place as where the additive and veterinary medical products were added.

3. Press line

A considerable amount of carry-over can occur in the press line. The carry-over increases as the press moulds are bigger. In addition, interim bunkers containing stocks can be a source of carry-over.

An item for attention is the return flows which are brought back directly into the pressed meal silo during pelletising.

4. Loading and transport

During storage, loading and transport of a finished product there will only be carry-over of any importance for highly critical additives and veterinary medical products (for example nicarbazine and sulfa-veterinary medical products). In these cases a mandatory working sequence should be used.

An item for attention is the processing of the sievings from the bulk load. Possible processing of such sievings must at least comply with the animal feed legislation and must therefore be processed in a careful and controlled fashion. Any sievings of medicated feed may not be reprocessed.

If the undesired carry-over of critical additives and veterinary medical products may be expected then company may take the following measures:

1. the drawing up of a mandatory production (working) sequence
2. additional measures in the event of product changes
3. the production of feeds with critical additives and veterinary medical products on another line
4. switching to less critical agents.

Measurement points for carry-over

The major causes of carry-over are the dosage / grinding / mixing line and the press line. The carry-over should be known if both feeds with critical additives and veterinary medical products as feeds with a maximum carry-over level are produced on these lines. In order to establish this reliably the following measurement points are important:

After the mixer, but as close as possible to the mixer for the measurement of the output content of the mixer:

a. at the entry to the pressed meal cell in grain production or the finished product cell in meal production, for the measurement of the carry-over on the dosage / grinding / mixing line
b. at the entry to the finished product cell in grain production for the measurement of carry-over on the press line.

Carry-over which is determined in this way is considered to be the installation carry-over.

Possible measurement substances

For the sake of reliability it is important to choose a measurement substance which can also be analysed properly at low levels. The following measurement substances are permitted. An indication is also given of to what degree of accuracy these means can be used to determine the carry-over in an installation.

Method	Chapter	Lower limit[1] of carry-over inspection accuracy in % [1)]
Cobalt chloride 100 ppm	5.4	1
Cobalt sulphate - 100 ppm - 50 ppm - 25 ppm	 5.4.1 4.2.1 4.2.2	 1 3 5
Protein/Manganese oxide	5.5	See the table in 5.5
FSS-Lake 100ppm	5.7	1
F-Lake 100 ppm	5.7	1
FSS-Lake 10 ppm	5.7	1
RF microtracer (by way of weighing)	5.8	1
Methyl violet	5.9	1

[1)] *Chapter5.6 includes a method for the measurement of the carry-over for the production system for premixes and feed additives*

Inspection report

Good reporting on the inspection is important to be able to apply the results unambiguously when determining measures and during supervision of the correct implementation. This should be based on a well thought out and properly described protocol which has been talked through in advance with those who will implement it and on a careful implementation of this protocol. At least the following items should therefore be laid down.

1. date
2. who is responsible for the carry-over inspection
3. description of the method used
4. a plan of the installation with an indication of
   a. grinding, mixing and press lines which were inspected
   b. the place where the measured substance was added
   c. sampling points
5. the number and size of the samples
6. the sampling time interval
7. analysis results
8. proper calculation of the carry-over
9. any sample pre-handling such as grinding, homogenisation, splitting and/or putting together

[1] *The lower carry-over limit is the carry-over percentage on which, using the method applied, a reliable statement can still be made. If the carry-over percentage is lower then at least the carry-over percentage stated here should be used.*

New measurement substances

New measurement substances will be admitted on the basis of examination where there has been validation with respect to the reference method (Cobalt method). The validation report must contain at least the following elements:

a. Name and address details of the submitter and inspection agency
b. Motivation/problem description
c. Characteristics with respect to the
    1. Animal feed installation to be used (including mixer/press installation/cooler)
    2. The reference measurement substances and the measurement substances to be examined
    3. Sampling plan for the samples to be taken in the various flush batches
    4. Sample preparation in the laboratory
    5. Analysis methods to be used
    6. Statistical methods to be used
d. Analysis results
e. Statistical processing of the analysis results
f. Conclusions
g. References

The report may be submitted for assessment by an expert panel to GMP+ International.

5.3 Process accuracy control procedure with cobalt (reference method)

1. FIELD OF APPLICATION

This testing procedure or method for the determining of the uniformity of meals and grains may be used on the usual premixes and mixes of ground compound feed raw materials in compound feed companies.

The method can also be used to obtain an indication of the carry-over which occurs in compound feed raw materials.

2. DEFINITIONS

Product installation: A product installation is an installation which is suitable for the preparation of compound feeds.

Cobalt mix: Cobalt mix is a mixture of wheat grits and Cobalt chloride hexahydrate in such proportions that the cobalt level in the cobalt mix is a minimum of 5% and a maximum of 6% and is prepared in accordance with the applicable standard working instructions as incorporated in § 17 of this inspection procedure.

3. PRINCIPLE

The control procedure for the determination of the degree of uniformity of meal mixes in the preparation of compound feeds makes use of a cobalt mix which, with respect to its properties, can replace the usual compound feed additives.

The control procedure includes the processing of three batches from the same feed mix. The first batch flushes the production installation and serves to determine the “natural” cobalt level in the feed in question. The cobalt mix (see section 2) is added to the second batch. The cobalt level of samples of meal and grains from the second batch is determined. The third production batch consists of the bare feed without the cobalt mix. The cobalt level of the meal and grain samples from this batch is also determined. This level gives a picture of the carry-over which is taking place in the production installation.

The cobalt content of the samples taken is determined using atomic absorption spectrometry (AAS) after heat destruction of the analysis sample at 550 degrees Celsius.

4. EQUIPMENT AND TOOLS

The following are required for the carrying out of the control procedure:

a. 110 plastic pots with lids with a size of 500 ml for saving the samples of meal and grains
b. a plastic scoop for taking the samples.

The number of pots specified is required if samples of meal are taken at one point in the production installation and samples of grains are taken at another point. For each extra sampling point 48 pots of 500 ml extra are needed.
There must be a laboratory which is able to determine cobalt level using atomic absorption spectrometry. Appointments should be made in good time with this laboratory for analyses to be carried soon after the samples are taken.

5. COMPANY DETAILS REQUIRED

The following will be requested in advance from a compound feed company at which a control procedure is to be carried out:

a. a block diagram of the production installation in which it can be indicated during the implementation where the cobalt mix has been added and where samples are taken.

The following will be requested during the implementation of the control procedure:

b. the computer prints or copies of them which show:
   1. the composition of the feed mix
   2. the batch weight requested by the computer, and
   3. the actual batch weight

or, if there is no computerisation:
   1. the composition of the feed mix
   2. the calculated batch weight from the sum of the quantities weighed per component
   3. the read-out of the actual batch weight.

The following will be requested to be able to calculate the batch weight for the mixer and the grain press:

c. where and how much molasses, vinasse and other liquid ingredients added to the main flow of the feed, and
d. where and how much fats, etc., are added to the main flow. The requested addition points are shown in the block diagram.

6. ADDITION OF THE COBALT MIX

A cobalt mix (see section 2) is added to the second batch of compound feed with a nominal cobalt level of at least 5% and maximum 6%.

The place where the cobalt mix is added depends on the carry-over path to be measured (see section 7.1). The place selected for the addition and for sampling should be shown in the block diagram for the product installation.
Add as much cobalt mix as corresponds to a dosage of 2.0 kg per ton of compound feed. The batch weight requested by the process computer may be assumed.

7. TAKING AND HANDLING SAMPLES

7.1 Company samples

7.1.1 Taking the samples

During the implementation of the control procedure in a compound feed company samples are taken at locations agreed in advance:
a. after the mixer but as close as possible to the mixer (see 13.1)
b. from the entrance to the finished product silo in the event of meal production or a pressed meal silo
c. from the entrance to the finished product silo in the event of grain production
d. another desired end point for the determination of the relevant carry-over path

If the meal or grain flow is not reachable at the desired locations then suitable openings should be made in consultation with the company.

Meal production
From the first batch only samples of meal immediately after the mixer are taken these being 10 samples for cobalt determination and another 4 samples for a fluid determination.

From the second batch 20 samples of meal (immediately after the mixer) and 20 samples of meal of 500 ml (from the input to the finished product silo) and 4 samples of meal (input to the finished product cell) are taken for the determination of fluid.

From the third batch 20 samples of meal (immediately after the mixer) and 20 samples of grains of 500 ml (from the input of the finished product cell) are taken for cobalt determination and another 4 samples of meal (after the mixer) and 4 samples of grains (input to the finished product cell) for the determination of fluid.

Grain production
From the first batch only samples of meal immediately after the mixer are taken these being 10 samples for cobalt determination and another 4 samples for a fluid determination.

From the second batch 20 samples of meal (immediately after the mixer) and 20 samples of grains of 500 ml (from the input of the finished product cell) are taken for cobalt determination and another 4 samples of meal (immediately after the mixer) and 4 samples of grains (input to the finished product cell) for the determination of fluid.

From the third batch 20 samples of meal (immediately after the mixer) and 20 samples of grains of 500 ml (from the input of the finished product cell) are taken for cobalt determination and another 4 samples of meal (immediately after the mixer) and 4 samples of grains (from the finished product cell) for the determination of fluid.

If a split is desired with respect to the carry-over by the dosage/grinding/mixing line on the one hand and the press line on the other hand then during the second and third batches another 20 samples of meal for cobalt determination and 4 samples of meal for fluid determination should be taken at the input to the pressed meal silo. The method of working is identical to the method for meal production.

Sample pots
All sample pots are provided with a sample code before the start of the production of the first batch of feed. Once the meal and/or grains flow starts for the batch to be inspected then 20 samples of meal and 20 samples of grains of 500ml are taken spread as well as possible over the duration of the batch. The sample pots must be filled up to the edge to avoid de-mixing (in the case of meal samples) as much as possible.

N. B.: It is very important that the samples are taken spread as well as possible over the duration of the batch in connection with the samples being representative of the batch as a whole.

7.1.2 Sample handling
Each meal and grain sample is ground in a suitable grinder. 90% of the result must pass through a 1.00 mm sieve and 50% must pass through a 0.50 mm sieve. Use sieves with round holes. Do not grind the samples finer than is necessary in order to avoid as much as possible the grinder heating up.

First grind the meal and grains samples from the first batch and then those from the third batch (carry-over batch) and finally the second batch of feed. In this way the samples are ground in ascending sequence of their cobalt level.

Clean the grinder after each sample using compressed air.

Clean the grinder after each group of 24 samples using both compressed air and, after disassembly of the relevant parts, by brushing clean with a brush which is not too soft. There may be no carry-over of material from the previous group of samples.

Homogenise each grinding as much as possible and then place it back in the original pot.

7.1.3 Storage of company samples
Company samples which are not inspected within a week of being taken should be stored in a refrigerated area.

7.2 Analysis of samples
The samples to be inspected which have been stored in a refrigerated area should be transferred at least 16 hours before the start of the inspection to the place where the inspection will take place. The sample packaging may not be opened during this period (see section 13.2). Act as indicated below once the specified period has elapsed.

Homogenise the mix to be inspected in the sample pot as much as possible by stirring it with a spoon or spatula.

From the company sample take 2 analysis samples of the desired amount.
Carry out the cobalt determination for both of the samples.

8. DETERMINATION OF THE FLUID LEVEL

The operational sample taken for the determination of fluid level is used for two analysis samples.

9. DETERMINATION OF THE COBALT LEVEL

9.1 Principle of cobalt determination
The determination of the cobalt level is done with the help of atomic absorption spectrometry (AAS) after heat destruction of the analysis sample measured by a filter of 240.7 nanometers after injection of this solution into the flame of the equipment.

A calibration graph can be made with the help of previously made solutions with an accurately known cobalt content. The extinctions measured in the analysis samples are converted into cobalt levels. The cobalt levels are expressed in parts per million (ppm).

The cobalt contents assigned to the analysis samples are corrected for the “natural” cobalt content determined in the samples of meal from the first production batch.

9.2 Standard samples
In the working instruction for the carrying out of the cobalt determination using atomic absorption spectrometry includes the inclusion of standard samples with a known cobalt content in each series of analysis samples. These standard samples serve as a check on the measured cobalt level.

9.3 Non-standard results
If the cobalt level of two analysis samples from the company sample deviates by more than 5% of the average measured values then two new analysis samples should be taken from the company sample and inspected (see 13.3).

10. PROCESSING OF THE RESULTS

10.1 Non-standard results
The results of the cobalt determinations in the compound feed from the three production batches will be assessed for deviations in as far as these are company samples of which more than two determinations have been done. In such cases a selection is made from the available results for the sample company sample of the two results with the least differences between them. These two results are then also included in the calculations. This avoids an analysis of variance with unequal degrees of freedom having to be carried out.

After the addition of the cobalt mix to the feed in the second batch the cobalt level in the first samples to be taken will be lower than in the subsequent samples [2]. This is because of a degree of carry-over from a bare floor from the first to the second batch of feed.

This may not be neglected in the determination of uniformity of the feed from the second batch. Although not statistically exact, the cobalt levels of the samples from the second batch are not assessed for a non-standard, average level of the results but they are all used for the calculation of the empiric coefficient of variation of the uniformity. That which was stated in the first sentence of this section does, however, continue to apply. The fact that the spread of the average results for the twenty samples is not “normal” but somewhat distorted is ignored.

An opposite effect is seen in the samples from the third batch of feed. Now the samples show a relatively high cobalt level as a result of carry-over of feed containing cobalt from the second to the third batch [2]. Normally the spread of the cobalt levels in the samples from the third batch is considerably more distorted than in the second batch. It is for this reason that the results of cobalt level determination in samples from the third batch are not checked for deviations. There is also no calculation of an empiric coefficient of variation for uniformity and it is enough to make a graph of the average cobalt level per sample against the sample number. In as far as the samples are properly representative for the whole batch which means they have been properly spread over the total duration, the average carry-over of cobalt can be calculated either in absolute terms or as a percentage of the level in batch two.

10.2 Conversion on the dry substance

The measured cobalt contents apply for the analysis samples or the operational samples with the existing fluid content (product basis). In order to be able to work further with the cobalt levels they should all be related to the dry substance.

Use the following formula for this conversion:

$$C = \frac{100}{100 - V} \times C1$$

Where

C	=	the cobalt content on the basis of dry substance in ppm
V	=	the fluid level of the group of operational samples involved in %
C1	=	the measured cobalt level on product basis in ppm.

The measured cobalt levels for dry substance will be decreased by the “natural” cobalt level for dry substance in the bare floor from the first batch.
The cobalt levels corrected in this way for dry substance will be used for the further processing of the results.

10.3 The carry-over

The carry-over for the installation is calculated as follows in accordance with this control procedure per measurement point.
The average cobalt level for dry substance in the group of company samples from the third batch divided by the average cobalt level for dry substance in the group of company samples from the second batch. By multiplying this figure by 100 the average carry-over percentage can be calculated.

10.4 The analysis of variance

The measured, corrected cobalt levels on the basis of dry substance from the samples in the second batch are used as elements in an analysis of variance. The results for meal and for grains are analysed separately.

In this analysis of variance the following sources of variation are distinguished:

a. the differences between the repetitions within the company samples, and
b. the differences between the sample averages from one group of company samples.

The results of the variation analysis are:
a. the standard deviation between repetitions (or within samples)
b. the standard deviation between sample averages (or between samples)
c. the average cobalt level per analysis sample
d. the average cobalt level per group of operational samples
e. the number of degrees of freedom associated with each of the standard deviations

The calculated standard deviations are converted to empiric coefficients of variation by multiplying the standard deviation by 100 and then dividing the product by the average cobalt level of the group of company samples. The empiric coefficient of variation calculated in this way between samples is a measure of the uniformity achieved at the measuring point.

This conversion is necessary because the standard deviation is greatly dependent on the cobalt level in the groups of operational samples.
The arithmetic implementation of the analysis of variance can be found in detail in nearly any manual on mathematical statistics. See, for example, [1].

The cobalt levels of the analysis samples from the third batch are shown in graph form against the number of the sample. These cobalt levels are not suitable for an analysis of variance because they can vary enormously and are usually not spread normally. The average cobalt level in the third batch can be calculated as specified in 10.3.

11. REPORTING

The following is reported for each group of company samples:
a. the average fluid content for the group of company samples (0.01%)
b. the average of the corrected measured cobalt levels on the basis of dry substance from each of the analysis samples (0.1 ppm at cobalt levels higher than 10 ppm and 0.01 ppm at cobalt levels of 10 ppm or less)
c. the average of the corrected measured cobalt levels of the company samples per group (0.1 ppm at cobalt levels higher than 10 ppm and 0.01 ppm at cobalt levels of 10 ppm or less)
d. the calculated carry-over of the installation in accordance with the control procedure.

A report is also made via each group of company samples from the first and second batches of feed of the following:
a. the standard deviations between repetitions (0.0001 ppm)
b. the standard deviation between sample averages (0.0001 ppm)
c. the number of degrees of freedom associated with the standard deviations as intended in 4. and 5.
d. the empiric coefficient of variation between repetitions (0.01 %)
e. the empiric coefficient of variation between sample averages (0.01%)

12. ASSESSMENT OF THE RESULTS

12.1 Repeatability of the cobalt determination

The empiric coefficient of variation between repetitions is a measure of the repeatability of the cobalt determination including sample treatment. The empiric coefficient of variation between repetitions amounts in properly conducted determinations to about 3 - 4% [2]. If the empiric coefficient of variation is greater then the implementation of the cobalt determination should be examined further.

The repeatability (r) is a factor 2.83 higher and therefore roughly amounts to 8.5 – 11.3%. This means that in the implementation of a determination in duplicate by the same analyst with the same equipment, on one in 20 case a difference is found between the two results which is greater than the value given for repeatability (r).

12.2 Uniformity of the material

The empiric coefficient of variation between sample averages is a measure of the uniformity of the meal mix or the grains from which the company samples have been taken. Statistically the group of company samples is not homogenous if the standard deviation between sample averages exceeds the standard deviation between repetitions by more than a given factor (F test). In very small standard deviations between repetitions this leads to a non-uniform mix although there is not yet any reason on technical grounds.

13. REMARKS:

13.1 First sample point

A feed mix is not uniform after the dosage of the various components. Even after the grinding of the raw materials in the hammer mill this is only partly the case. Often finer raw materials are led around the hammer mill and carried straight to the mixer. A uniform feed mix may therefore only be expected for the first time in the mixer. Taking samples directly from the mixer is difficult and may be dangerous and is certainly not recommended. The sample point after the mixer should therefore be used. In most companies this will be the outflow of the bunker under the mixer.

13.2 Acclimatisation of company samples

Company samples which can not be examined in the short term should be stored in a refrigerated area to prevent decay. These samples must be brought to the area where the inspection will actually take place well in advance. This allows the company sample to reach the temperature of the laboratory. This method of working prevents sample material from being exposed to condensation from the warmer air in the laboratory. Condensation makes it impossible to determine the correct fluid content of the sample. A non-homogenous distribution of the condensed fluid in the sample material will also cause a greater spread of the results of the cobalt determination.

13.3 Non-standard results of cobalt determinations

If two cobalt determinations from the analysis samples from the same company sample differ by more than 5% in value then two new analysis samples must be tested.
This procedure usually results in one of the four results being rejected. In addition to company samples with results of two analysis samples there are also samples with three or sometimes four non-deviating results. This makes the implementation of the analysis of variance difficult. Statisticians have developed methods of calculation to replace more than two valid results with two results which contribute in the same way to the variance of the results.

As a judgement on whether or not a mix is uniform rests on a technological agreement on the limit value for the empiric coefficient of variation, it has been decided to simplify the method.

From the set of three or four results of which one (or two) are deviating, the deviating results are rejected.
If three valid results remain then the two results with the least difference between them are used. In this way the variance analysis consists of two company samples each with two repetitions.

14. SAFETY

The control procedure is usually carried out in practice in a compound feed company.

For those who carry out the control procedure in a compound feed company the following safety rules apply:

a. the operatives will make themselves aware before the start of the work of the safety instructions which apply in the compound feed company
b. during their stay in the compound feed company the operatives are bound to follow the safety instructions of the compound feed company
c. during the adding of the premix containing cobalt to the main flow of feed protective gloves and a respiratory protector in the form of a nose covering is to be worn.

15. PROCESSING OF COMPOUND FEED CONTAINING COBALT

The mix containing cobalt is added to the second batch of feed produced for the control procedure at a dosage of 2 kg per ton of feed. The compound feed will then contain about 100 ppm of cobalt. This feed should be stored in a separate cell and may not be traded.
It is recommended that the feed containing cobalt is diluted such that the cobalt concentration in the final feed intended for trading amounts to no more than 2 ppm. Account should be taken when doing this of the cobalt level already present in the raw materials.

The feed from the third batch usually contains only slight amounts of cobalt. As the degree of carry-over is not known in advance, account must be taken of fairly large deviations in the cobalt level of this feed. It is advisable also to store this feed separately and to dilute it sufficiently.

If the compound feed company does not wish to use this feed in any way then it must be treated as chemical waste and handled and removed as such.

16. LITERATURE

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17. STANDARD INSTRUCTION FOR THE PREPARATION OF COBALT MIX

Introduction

The cobalt mix for the carrying out of the control procedure is prepared wet from wheat grits and cobalt chloride hexahydrate. This ensures that the cobalt is well distributed over the cobalt mix and that the cobalt mix does not differ much with respect to its characteristics from the compound feed.

Ingredients

a. wheat grits, well defined quality, as bearer
b. cobalt chloride hexahydrate, minimum 99% pure
c. water of at least mains water quality

Equipment

a. mixing equipment, suitable for dry and wet products, for example the Nauta mixer with clump breaker
b. equipment for spraying under pressure (compressed air)
c. drying equipment with forced ventilation
d. grinding equipment including a high-revolutions grinder
e. sieving equipment.

Safety measures

When working with cobalt, especially when spraying, grinding and sieving, mouth and nose protection should be used and suitable gloves of synthetic material should be worn.

Preparation of the cobalt mix

The required amounts of cobalt chloride hexahydrate and wheat grits are weighed. The cobalt chloride hexahydrate is dissolved in about twice the amount of water. The mix is slightly warmed if necessary (max. 50 ^{o}C) until a clear solution is obtained. The solution is transferred into the pressure vessel of the spraying equipment. The weighed wheat grits are put into the mixer, the mixer is then started and the pressure vessel is put under pressure (c. 2 – 2.5 bar). The supply to the sprayer in the mixer is opened so that the solution is atomised. Once the cobalt chloride hexahydrate solution has been completely atomised, possibly in two or more steps depending on the volume of the pressure vessel, all the equipment which was used three times for the preparation of the cobalt solution and the atomisation must be flushed with a suitable amount of water. The wet cobalt mix is mixed for a further 15 minutes.

After this the mixer is emptied as much as possible and the mixture is dried for 24 hours at c. 60 ^{o}C dried?

The dried material is ground with a high-speed grinder (for example a pin crusher) and then sieved with a mesh of maximum 500 um. The residue from the sieving can be ground again and sieved again with the same sieve.

That which falls through is put together, homogenised in a mixer and hermetically packed, preferably in a quantity which is suitable for immediate use in the testing procedure (i.e. 2 kg/ton).

The packaging states:
a. the name of the product (cobalt mix)
b. filled weight
c. production date and batch and report number
d. the nominal cobalt concentration
e. the sequence number of the packaging in the batch
f. safety measures.

Account must be taken of the fact that the dried cobalt mix is to some extent hygroscopic. It is advisable to work in a dry environment with the least possible exposure to air.

Sampling and reporting
A minimum of four samples are taken from each homogenised batch during the packaging of the cobalt mix. Two of these are intended for a moisture determination and one for the determination of the particle size distribution while at least one is kept as a reserve sample.
The report on the cobalt mix prepared in this way will contain at least:
a. the origin and characterisation of the wheat grits
b. the origin and purity of the cobalt chloride hexahydrate
c. the quantity of carrier, cobalt salt and water used
d. the average moisture content of the mix after homogenisation
e. the calculated cobalt level of the cobalt mix
f. the particle size distribution of the cobalt mix.

5.4 Testing procedure for carry-over in compound feed preparation using cobalt mixes

This chapter describes a number of alternative procedures for in-company measurement of carry-over using cobalt tracer. These are a simplification of the reference method described in Chapter 2.2

On the one hand it is a procedure in which the number of samples to be taken and analysed can be considerably reduced to that which is strictly necessary for a reliable measurement of carry-over. This particularly limits analysis costs. The company is of course free to take and analyse more samples in order to gain more insight into the process accuracy of the installation.

On the other hand, two procedures are involved in which the cobalt level is lowered by a factor 2 to 4 respectively. This limits the problems of responsible processing of the batch of feed to which the cobalt has been added. It also limits, however, the sensitivity of the method. Very low to relatively low carry-over levels (< 3%, resp. < 5%) are not properly measured with this.

For in-company measurement of carry-over with a reduced cobalt level use may be made of both the reference method specified in chapter 2.2 and the above-mentioned procedure with a reduced number of samples.

For the inspection procedures specified in both chapter 2.3.1 and chapter 2.3.2 a mix based on cobalt sulphate may be used instead of the cobalt mix defined in § 17 in chapter 2.2. The mix on the basis of cobalt sulphate should be prepared in accordance with the standard instructions in chapter 2.3.4.

5.4.1 Modification of the reference method with cobalt for the in-company measurement of carry-over of 1% and more in compound feed mixing (reduced number of samples).

Both the reference method (see chapter 2.2) and this modified procedure can be used to measure a carry-over of 1% or more in the preparation of mixed feeds. Essential in this is the minimum content of 5% cobalt in the cobalt mix to be used and the subsequent content of at least 100 ppm in the feed mix to which the cobalt mix is added.

This description indicates where and in what regard the reference method (chapter 2.2) may be modified for in-company measurement of carry-over. For the sake of simplicity the numbering of chapter 2.2 will be used. Parts of the reference method which are not mentioned remain unchanged in theory or only subject to minor, obvious amendments.

1. FIELD OF APPLICATION

This method is only intended for in-company measurement of carry-over.

2. EQUIPMENT AND TOOLS

At least 46 plastic pots of 50 ml with a lid or plastic sample bags of 1 litre are required.

3. TAKING AND HANDLING SAMPLES

3.1 Taking samples

The following schedule can be used when taking samples in which part of the sampling and/or further handling is voluntary if it is desired to obtain more insight.

a. After the first batch (without added cobalt):
   1. at least 4 samples at the selected control point for carry-over. Preferably after the cooler for the determination of the natural cobalt level in the feed(KAC1 – KAC4)
   2. at least 4 samples at the same control point for the determination of the moisture level (VAC1 – VAC4).

b. After the second batch (with added cobalt mix):
   1. at least 10 samples, as close as possible after the mixer and regularly distributed over the outflow of a batch for the determination of the average cobalt level (KBM1 – KBM10). Possibly (this is voluntary) 20 samples may be taken (see section 7.2.3)
   2. at least 4 samples at the same point for the determination of the moisture level (VBM1 – VBM4)
   3. possibly (this is voluntary) 10 samples at the specified control point(s) for carry-over for the determination of the average cobalt level (KBC1 – KBC10).

c. After the third batch (carry-over batch)
   1. possibly (this is voluntary) 10 samples as close as possible after the mixer, regularly distributed over the outflow of a batch (KCM1 – KCM10)
   2. 20 samples at the specified control point(s) for carry-over, regularly distributed over the total duration of the batch at this point for the determination of the degree of carry-over (KCC1 – KCC20)
   3. at least 4 samples at the same point for the determination of the moisture level (VCC1 – VCC4).

3.2 Sample handling and destination

The technical sample handling (grinding, sequence, etc.) remains as described in chapter 2.2. The following applies with respect to the destination of the samples.

a. All moisture samples have the function that the results of the cobalt analyses for differences in moisture content may be corrected or recalculated for dry substance.

b. The samples KAC1 – KAC4 are analysed individually in duplicate. This is – especially for the third batch – of great importance because the cobalt levels in batches two and three must be corrected for the “natural” cobalt level in the feed.

c. Samples KBM1 – KBM10 can serve two purposes. Each sample can if desired be split into a ‘a’ and a ‘b’ sample, or, if 20 samples are taken instead of 10 (see section 7.1.2), these can be used in turn or each can be split for one purpose or another.
d. Possibly (this is voluntary), one half of the samples can now be used to determine the uniformity of the mix. To do this the 10 (or 20) samples must each be analysed separately in duplicate.

e. A mix can be made of the other half of the 10 or 20 samples possibly after further reduction of the product which is used to determine the average cobalt level of the second batch. To do this at least two new samples are taken from the mix in which the cobalt level and the moisture level are analysed in duplicate. Naturally, the average cobalt level of batch two may also be determined by averaging the individual duplicate results of the 10 or 20 samples.

f. Using samples KBC1 – KBC190 an impression can be obtained (this is voluntary) of the extent to which the uniformity obtained immediately after mixing (KBM1 – KBM10) in the subsequent production and transport process is maintained up to the control point for carry-over. These samples must each be separately analysed in duplicate.

g. Using samples KCM1 – KCM10 a determination may possibly be made (this is voluntary) the extent to which carry-over is already occurring in the path up to the sampling point immediately after the mixer. For the analysis a choice can be made to analyse a mix sample (analysis of two samples in duplicate for the average carry-over), or of all ten samples separately in duplicate (carry-over pattern and calculation of the average).

h. The samples KCC1 – KCC20 may be mixed two at a time, thus KCC1 + 2, KCC3 + 4 etc., after which in each of the 10 new samples in duplicate the cobalt level is determined. Assuming that each of the original samples is representative for an equivalent part of the batch, the average carry-over can be directly calculated. If it is known that this is not the case, for example because of irregular time intervals between sampling, the weighted average, related to the actual time intervals, is calculated.

i. It may also be decided to analyse each of the samples KCC1 – KCC separately and then to calculate the average as described above.

4. PROCESSING OF THE RESULTS

4.1 Variance analysis

In this simplified implementation the results are only suitable to a limited extent for statistical analysis.
In as far as there are measurement series with analyses carried out in duplicate, it is advisable in any event to calculate via a variation analysis the empiric coefficient of variation between repetitions per measurement series.
In as far as there are measurement series for which in an ideal case the results must have the same value (uniformity), an analysis of variance must be carried out with which both the empiric coefficients of variation between samples as well as between repetitions is calculated.

This applies in particular to the sample series KAC1, KAC4 and possibly for KBM1 – KBM10, KCB1 – KBC10 and KCM1 – KCM10 in as far as one takes samples from these series, individually analyses them and is interested in the degree of uniformity.

4.2 Calculation of carry-over

All cobalt levels are corrected in advance using the average results of the corresponding moisture determinations for dry substance. The carry-over for the installation is now calculated as follows on the basis of the corrected values:
the average cobalt level in the 20 samples KCC from the third batch minus the average cobalt level in the 4 samples KAC from the first batch, divided by the average cobalt level from the 10 samples KBM from the second batch, also minus the average cobalt level in the 4 samples KAC from the first batch. By multiplying the result by 100 an average percentage carry-over in the batch immediately following the batch to which the cobalt mix was added as a model for a premix with additive can be calculated.

By displaying the results of the cobalt analyses in the samples KCC1 – KCC20 (corrected for the average of KAC1 – KAC4) in graphic form, a carry-over pattern is obtained which gives in principle more information than the calculated average.

4.2.1 Modification of the measurement methods with cobalt for the in-company measurement of carry-over of 3% and more in compound feed mixing

For the in-company measurement of carry-over of 3% or more, either the testing procedure described in chapter 2.2 or the modified procedure described in chapter 2.3.1 is used. Use is made of a cobalt content in the cobalt mix as specified in section 2 of chapter 2.2 of minimum 2.5%. This realises a level of about 50 mg/kg in the second batch of feed in the testing procedure.

4.2.2 Modification of the measurement methods with cobalt for the in-company measurement of carry-over of 5% and more in compound feed handling

For the in-company measurement of carry-over of 5% or more, either the testing procedure described in chapter 2.2 or the modified procedure described above in chapter 2.3.1 is used. Use is made of a cobalt content in the cobalt mix as specified in section 2 of chapter 2.2 of minimum 1.25%. This realises a level of about 25 mg/kg in the second batch of feed in the testing procedure.

Literature

1. Beumer, H.; Nieman, W.. Toetsingsprocedure procesnauwkeurigheid met behulp van kobalt. Consequenties van een lager kobaltniveau. CKD werkgroep Toetsingsprocedure procesnauwkeurigheid May 1992, ref. 630.95/0168/Bm-Hb.

4.2.3 Standard instruction for the preparation of a cobalt sulphate mix for the in-company measurement of carry-over

Introduction
The cobalt mix for the carrying out of the testing procedure is prepared via dry mixing from wheat grits, wheat red dog and cobalt sulphate. This ensures that the cobalt is well distributed over the cobalt mix and that the cobalt mix does not differ much with respect to its characteristics from the compound feed.

Ingredients
a. wheat grits and wheat red dog, well defined quality, as bearer
b. cobalt sulphate heptahydrate, minimum 98% pure

Equipment
mixing equipment, suitable for dry products, such as Planet mixer.
Also needed as tools are, among others, suitable balances for weighing the ingredients.

Safety measures
When working with cobalt, mouth and nose protection should be used and suitable gloves of synthetic material should be worn.

Preparation of the cobalt mix
The required amounts of cobalt sulphate heptahydrate, wheat grits and wheat red dog are weighed.
The weighed quantities are mixed in a Planet mixer for 15 minutes. The mix is then measured into buckets of 2.0 kg and properly closed off with a lid.

The packaging states:
a. name and code of the product (cobalt mix)
b. filled weight in kg
c. date of production
d. the nominal cobalt concentration
e. the sequence number of the packaging in the batch
f. safety measures.

The closed buckets should be stored under air-conditioned conditions.
Open the packaging immediately before use.

The cobalt mix should comply with the following requirements:
a. particle size: maximum 1% > 0.7 mm; maximum 10% > 0.5 mm
b. cobalt level: at least 4.5%

Sampling and reporting

Four 4 samples are taken from each homogenised batch during the packaging of the cobalt mix. Of these 1 is intended for moisture determination, 1 for the determination of particle size distribution and 1 for the determination of cobalt, while 1 is kept as a reserve sample.

The report on the cobalt mix prepared in this way will contain at least:

a. the origin and characterisation of the wheat grits
b. the origin and characterisation of the wheat red dog
c. the origin of the cobalt sulphate heptahydrate
d. the amount of carrier and cobalt salt used
e. the moisture content of the mix after homogenisation
f. the calculated cobalt level of the cobalt mix
g. the analysed cobalt level of the cobalt mix
h. the particle size distribution of the cobalt mix.

5.5 Testing procedure for the carry-over in compound feed mixing using a mix of manganese oxide and a protein-rich and a protein-poor mix

1. APPLICATION AREA

The testing procedure was developed for the determination of the carry-over which occurs in compound feed production companies. The carry-over of large components from the batching equipment for raw materials and the carry-over of the components which are added via the premixes are determined separately.
By collecting the samples which have been taken for the carry-over inspection at various different places in the production process, insight can be obtained into the carry-over in components of the production process (for example: grinding / mixing line to pressed meal bunker or the press / cooling line). The method is also suitable for the determination of the extent to which uniform mixes can be produced using the installation (see item 9).

2. DEFINITIONS

Carry-over
Carry-over means that part of the previous batch of feed remains in the production and transport system and gets into the following batches.

Carry-over level
The carry-over level is defined as the amount of a nutrient of component from a previous batch, expressed as a percentage, which gets into the following batch of feed (of the same size). The carry-over level can be measured for a section of the installation (for example the pressed meal bunkers) or for the whole installation.

3. PRINCIPLE OF THE TESTING PROCEDURE

The testing procedure is carried out by first fabricating a protein and Mn-rich Soya mix and immediately afterwards by fabricating a protein and Mn-poor mix on the same production line. The increase in the protein and Mn level of the maize mix during the running of the production line is caused by carry-over. By relating this increase to the protein and Mn level of the Soya mix, the carry-over level can be calculated.
Because the protein and manganese oxide content of the maize mix progresses hyperbolically (from high levels at the beginning of the flow to lower levels afterwards), the sampling procedure must be given particular attention.

4. EQUIPMENT AND TOOLS

The following are required for the carrying out of the testing procedure:
a. a quantity of manganese oxide corresponding to 0.4% of the usual batch size
b. (possibly) a scoop for taking samples
c. two buckets to be able to collect a number of sub-samples
d. sample pots or bags which can hold at least 200 grams of material. If the carry-over inspection is carried out at two places in the production line then 20 sample pots will usually be enough (only 14 samples will actually be tested).

5. COMPANY DETAILS REQUIRED

The following must be known about the company where the testing procedure will be carried out:

a. the block diagram of the production installation
b. the way in which the Soya and maize mix is put together. An exact indication should in particular be given of how and where the manganese oxide is added and how any transport system for the manganese oxide to the mixer is flushed both for the Soya mix and for the maize mix.

6. IMPLEMENTATION OF THE TESTING PROCEDURE

6.1.a. Fabrication of the protein and Mn-rich Soya mix

The Soya mix (with the usual batch size) consists of 92% Soya meal, 4% fat, 3% cane molasses, 0.4% manganese oxide and 0.8% dicalcium phosphate (or chalk or salt). This mixture is batched, ground, mixed and pelletised in the usual way. Molasses and fat are added to obtain a meal with normal physical characteristics which can be pelletised properly. The Soya meal may come from more than one batching silo.
The manganese oxide comes instead of the premix and should take the same route as the premix. The manganese oxide is therefore batched into the premix weighing machine or dumping pit.
The batching should be carried out such that the manganese oxide comes virtually fully to the bottom of the premix weighing machine or dumping pit.

The manganese oxide should comply with the following requirements:

a. Mn level at least 50%
b. particle size: 100% should be smaller than 0.2 mm.

Normally, chalk, salt and/or feed phosphate is batched via the same weighing machine or dump pit. Because of this the carry-over of components from the premix will be less especially when first the premix and only then the other products are batched.
For the testing procedure first 0.4% manganese oxide and then 0.8% chalk, feed phosphate or salt is batched.
Once the content of the premix weighing machine (or the dumping pit) has been added to the Soya mix in the mixer, the normal mixing time is carried out. The mix is then removed to an empty pressed meal bunker and pelleted (sample).
The grinding/mixing line and the press/cooling line may not be used for anything other than the maize mix after the Soya mix.

6.1.b. Sampling of the Soya mix

When unloading the Soya pellets in the finished product silo a good mix sample is taken from the last part of the batch.

6.2.a. Fabrication of the protein and Mn-poor maize mix

The maize mix (with the same batch size as the Soya mix) consists of 92% maize, 4% fat, 3% cane molasses and 0.8% dicalcium phosphate (or chalk or salt). If it is not possible to batch 92% maize then a maize/wheat mix or another protein-poor mix may be put together (sample).
The transport system between the premix weighing machine (or dumping pit) and the mixer is flushed with 0.8% dicalcium phosphate (or salt or chalk).
The mixing time starts once the feed phosphate has been added to the mix. The mix is then removed to the (empty) pressed meal bunker (sample) and then pelletised (sample).

6.2.b. Sampling of the maize mix

The following samples of the maize mix are collected:

a. the maize (and possibly the wheat) which is used for the composition of themix
b. six samples from the maize mix at the inflow to the pressed meal bunker
c. six samples from the maize mix at the inflow to the final product silo.

The sampling procedure is important for the samples in II and III. In particular the first part of the meal or the pellets from the batch will have higher levels of protein and manganese oxide which will then decrease relatively quickly to a lower and more constant level. It is therefore important to sample the first part of the meal or pellet flow intensively and to know to which part of the feed these samples relate.

The sampling procedure at the inflow to the pressed meal bunker (which usually lasts 3 to 5 minutes) is as follows:

a. during the first 30 seconds as many sub-samples as possible are collected in a bucket; a mix sample is made from these
b. for the second 30 seconds: idem
c. then every 30 seconds a random sample from the flow is collected until the meal flow stops.

The total running time of the meal flow is noted and 6 samples are kept, namely the three which were taken first and three of the other samples.

The sampling of the pellets at the inflow to the finished product silo takes place in the same way. Because the total duration is usually somewhat longer the procedure is now as follows:

a. during the first minute as many sub-samples as possible are collected in a bucket; a mix sample is made from these
b. during the second minute: idem
c. then every minute a random sample from the flow is collected until the pellet flow stops.
d. (If the pellet flow is not continuous then the “real” duration should be used.)

Note the total duration here as well and keep six samples, namely the three which were taken first and three of the other samples.

6.3 Processing of the Soya mix in compound feed

At low carry-over levels the Soya mix has a Mn level of c. 2,000 mg/kg. In the processing of this Soya mix in compound feed account should be taken of the fact that the Mn level of compound feed may be a maximum of 250 mg/kg.

7. THE ANALYSIS OF THE SAMPLES

In total there are 14 (or possibly 15) samples collected:

1 sample of Soya pellets (+ Mn)	= A
1 sample of maize (pure) (+ possible wheat)	= B
6 samples of maize mix meal (pressed meal bunker)	= C (1 to 6)
6 samples of maize mix meal (finished product silo)	= D (1 to 6)

All samples are analysed for RE and Mn.
Half of the samples of maize meal mix and maize mix pellets are analysed for moisture; this is in order to find out whether the moisture content has changed during pelletising. If the moisture content has clearly changed during pelletising then the RE and Mn levels of the maize mix pellets should be corrected for the moisture content of the maize mix meal.

8. THE CALCULATION OF THE CARRY-OVER PERCENTAGES

The carry-over percentages can be calculated from the levels of RE and Mn in the samples taken. Suppose that the following levels are found:
Soya pellets: 420 grams RE and 2,006 mg Mn/kg
Pure maize: 86 grams RE and 4 mg Mn/kg
samples maize mix (above the pressed meal bunker)

1.	mix sample (0.5 min.)	160 grams REand	400 mg Mn/kg	
2.	mix sample (0.5 min.)	100 grams REand	60 mg Mn/kg	
3.	random sample	90 gram	and	27 mg
4.	random sample	85 grams (avg. 88)	and	30 mg (avg. 28)
5.	random sample	88 gram	and	28 mg
6.	random sample	89 gram	and	27 mg

The total duration of the meal flow in the pressed meal bunker = 5.5 min.

Expected levels of maize mix (92% maize and 3% molasses with 40 grams RE and 25 mg Mn/kg):

RE	=	0,92* 86 + 0,03*	40 =	80,3	gram/kg
Mn	=	0,92* 4 + 0,03*	25 =	4,4	mg /kg

The average levels of RE and Mn in the maize mix are calculated as follows:

RE	=	0,5/5,5* 160 + 0,5/5,5* 100 +	4,5/5,5*	88	=95.6 grams/kg
Mn	=	0,5/5,5* 400 + 0,5/5,5* 60 +	4,5/5,5*	28	= 64.7 mg/kg

(samples 1 and 2 each have a duration of 0.5 minutes from a total duration of 5.5 minutes.
For samples 3 to 6 the average level is calculated; the duration of this is 5.5 – 2 x 0.5 = 4.5 minutes).

The carry-over percentage (Vs-%) is now calculated as follows:

$$Vs\text{-}\% = \frac{\text{avg. level in maize mix} - \text{expected level in maize mix}}{\text{avg. level in Soya pellets} - \text{expected level in maize mix}} \times 100$$

The carry-over percentages are then (up to the pressed meal bunker)

$$\text{for RE} = \frac{95{,}6 - 80{,}3}{420 - 80{,}3} \times 100 = \frac{1.530}{339{,}7} = 4.5\%$$

$$\text{and for Mn} \frac{64{,}7 - 4{,}4}{2.006 - 4{,}4} \times 100 = \frac{6.030}{2.001{,}6} = 3\%$$

The carry-over percentages at the inflow to the finished product cell are calculated in the same way.
The carry-over percentage of the RE relates to the feed as such, from the batching equipment.
The carry-over percentage for the Mn gives an indication of the carry-over of components from the premix.

9. THE MEASUREMENT OF UNIFORMITY

In order to determine the extent to which the installation produces uniform mixes, at least 10 samples should be collected from the Mn-rich Soya mix and analysed for Mn. The spread of the Mn levels of these samples (standard deviation or the difference between the highest and lowest value) is a measure of uniformity.

When taking the samples from the Soya mix one should ensure that the whole flow of the mix is sampled. Because it is often not known exactly how long the meal flow will last, it is desirable in the first instance to take a generous number of samples of which only a part (namely 10) need to be tested.

The uniformity test may be carried out at many places in the installation. If the samples are taken immediately after the mixer then a good picture is obtained of the functioning of the mixer.
If, on the other hand, samples are taken at other places in the installation (but after the mixer) then the uniformity will generally be less than immediately after the mixer.

This is because in this case de-mixing and carry over also play a role. Because the Mn-rich Soya mix is always produced after a “normal” compound feed with much lower Mn levels, the first samples of the Soya mix will be contaminated with a certain amount of compound feed and will therefore contain less Mn. The subsequent samples will be contaminated with less and less normal compound feed and will have higher and higher Mn levels.

10. ERRORS DISCUSSION

Table 1 shows which Mn and protein levels are to be expected in the maize mix at the various carry-over percentages, assuming 80 grams RE and 5 mg Mn/kg maize mix (pure) and 400 gram RE and 1,800 mg Mn/kg Soya mix.

Table 1 Effect of carry-over percentage on Mn and protein level of the maize mix.						
Carry-over %	0	1	3	5	10	15
MN from basis*	5	5	5	5	5	5
From Soya	0	18	54	92	180	270
	5	23	59	95	185	275
* effect of thinning discounted						
RE from basis	80	79,2	77,6	76	72	68
From Soya	0	4	12	20	40	60
	80	83,2	89,6	96	112	128

On the basis of the analysis accuracy of the Mn and RE determination an estimate can be made of the accuracy with which the carry-over percentage can be determined.

For the 6 maize samples to be tested it is assumed that the average Mn-level found in 95% of the cases will lie between 95 and 105% of the actual level; for levels < 60 mg/kg the absolute interval is made equal to the interval for
60 mg/kg, thus +/- 3 mg/kg.
For the Soya mix it is assumed that the Mn level found in the analysis will deviate by a maximum of 100 mg/kg from the actual level.
For the protein it is assumed that the average level found for the 6 maize samples will in 95% of cases lie between 99 and 101% of the actual level and that the level found for the Soya mix will deviate by a maximum of 2% from the actual level.

The results of the calculations are shown in Table 2.
It may be concluded that low carry-over percentages can be determined fairly reliably.
For low carry-over levels Mn seems to comply better than the RE; at high carry-over levels, on the other hand, the protein gives better results than the Mn.

Table 2: Effect of the analysis accuracy on the carry-over percentage to be established				
		Maize mix		
Carry-over level		Calculated	Interval analysis	Carry-over percentage*
Mn	0	5 mg/kg	2 - 8 mg/kg	0,16 - 0,18%
	1	23	20 - 26	0,8 - 1,2
	3	59	56 - 62	2,7 - 3,4
	5	95	90 - 100	4,5 - 5,6
	10	185	176 - 194	9 - 11,1
	15	275	261 - 289	13,5 - 16,7
On the basis of 1800 mg Mn/kg Soya mix (variation 1700-1900, at low Mn in maize there is a calculation of high Mn in Soya, and vice versa).				
		Calculated	Interval analysis	Carry-over %*
RE	0	80 g/kg	79.2 - 80.8 g/kg	- 0,25 - 0,25
	1	83,2	82,4 - 84,0	0,7 - 1,3
	3	89,6	88,7 - 90,5	2,6 - 3,4
	5	96	95,0 - 97,0	4,5 - 5,5
	10	112	110,9 - 113,1	9,4 - 10,6
	15	128	126,7 - 129,3	14,2 - 15,8
On the basis of 400 g RE/kg Soya mix (variation 392-408, at low RE in maize there is a calculation of high RE in Soya, and vice versa).				

5.6 Testing procedure for the measurement of carry-over in premix and additives installations

1. SYSTEM

The method of measurement of carry-over in premix and additives installations corresponds as far as the systematics are concerned to Chapters 2.2 to 2.4.

2. CARRY-OVER PROCESS

a. The carry-over process to be measured relates to the point where the additives and/or animal veterinary products are added to the bulk vehicle load or the bag filling.
b. Measurement of the carry-over should be carried out for each production line in the installation.
c. The measurement should be carried out with a quantity of mix which is equal to the smallest batch which in practice may be produced on the production line in question.

3. TRACER SUBSTANCE TO BE USED

The following tracer substance can be used for the measurement of carry-over: cobalt mixes in accordance with Chapter 2.2 or 2.3.4 with a cobalt concentration of at least 200 mg/kg. At cobalt concentrations of 2,000 mg/kg or more use may also be made of pure cobalt sulphate. In addition the microtracers FSS-Lake and F-Lake and methyl violet can be used in the dosage of 10 mg/kg. Otherwise there should be compliance with Chapter 2.3.4.

4. DETERMINATION OF CARRY-OVER

The measurement of carry-over is done by taking the mix in which the carry-over occurs into consideration as a whole. This means that the average level in this mix is the departure point for determining the carry-over. The carry-over is measured as follows:

a. mix the whole mix again
b. take and analyse 5 samples from this mix (V1 to V6). The average level is calculated from this
c. The carry-over is measured as follows:

$$\frac{\text{(average quantity in mix in which carry-over occurs)}}{\text{(batching in previous mix from which there is carry-over)}} \times 100\%$$

5.7 Checking procedure for the process accuracy of compound feed with micro tracers

1. FIELD OF APPLICATION

This testing procedure or method for the determining of the homogeneity of meals and grains may be used on the usual premixes and mixes of ground compound feed raw materials in compound feed companies.

The method can also be used to obtain an indication of the carry-over percentage which occurs in compound feed raw materials.

2. DEFINITIONS

Production plant: A production plant is an installation which is suitable for the preparation of compound feeds.

Microtracer mix: For the testing of a compound feed the microtrace mix contains 4 kg feed lime or wheat grits and 100 g microtracer. Therefore 100 g microtracer is mixed with 1 t compound feed, which corresponds to a mixing accuracy of 1:10 000.
For the testing of a premix the microtrace mix contains 4 kg feed lime or wheat grits and 10 g microtracer. Therefore 10 g microtracer is mixed with 1 t compound feed, which corresponds to a mixing accuracy of 1:100 000.

3. PRINCIPLE

So-called microtracers are used as a measuring substance. These are elementary iron particles which are coated with a feed colourant in order to be able to count the colour points in the analysis. An average number of particles per mg is indicated in the analysis certificate for the microtracer used. For the microtracer particles it is a case of particle distribution thus the average number of particles varies depending on the microtracer batch. In order to determine the number of particles in question in the test a microtracer mix is produced in which the average number of particles is determined exactly for the microtracer used (see section 17).

Two different microtracers are suitable for the homogeneity and carry-over analysis. These are distinguished by their particle size and therefore the number of particles per mg. Microtracer F consists of particles with a size distribution of 150 – 300 µm and have been used for some time in the feed industry. The somewhat finer microtracer FSS with a size distribution of 75 – 150 µm was specially developed for chicken feeds to decrease the test quantity used.

The required accuracy for the determination of carry-over of 1% is achieved in both microtracer F and FSS. In order to achieve a statistically accurate assessment, a minimum number of 15 particles must be present per filter. Only then can an accurate assessment of homogeneity be made for the first production batch.

Method	Average number of particles per milligram [mg]	Test quantity for the assessment of homogeneity [g]	Average expected number of particles in the tested quantity	Test quantity for determination of carry-over [g]	Accuracy of the carry-over examination in %	Average expected number of particles in the tested quantity
FSS-Lake 100 ppm	200	2	40	200	1	40
F-Lake 100 ppm	25	20	50	2000	1	50
FSS-Lake 10 ppm	200	25	50	2500	1	50

Table 1:

The control procedure for the determination of the degree of homogeneity of meal mixes in the preparation of compound feeds makes use of a microtrace mix which, with respect to its properties, can replace the usual compound feed additives.

The control procedure includes the processing of two batches from the same feed mix. The microtrace mix (see section 2) is added to the first batch. The number of particles of microtracer in the samples of meal and grain from the first batch of feed is then determined. The second production batch consists of the bare feed without the microtracer mix. The microtracer level of the meal and grain samples from this batch is also determined. This level gives a picture of the carry-over which is taking place in the production installation.

The number of particles of microtracer in the samples which were taken is determined by separating the microtracer particles from the other feed particles using a rotary detector and by using the feed colourant to make the separate microtracer particles visible on a sheet of filter paper.

4. EQUIPMENT AND TOOLS

The following are required for the carrying out of the testing procedure:

a. 40 plastic sample bags for keeping the samples of meal and grain each with a capacity of twice the quantity of the sample (see table 2)
b. 40 plastic sample bags for keeping the samples of meal and grain each with a capacity of twice the quantity of the sample (see table 2)
c. one small and one large plastic scoop for taking the samples.

The number of bags specified is required if production plant samples of meal are taken at one point in the production installation and samples of grains are taken at another point. For each subsequent sampling point 40 bags extra are needed.

Method	Sample quantity to be taken from production batch 1 for the determination of homogeneity	Sample quantity to be taken from production batch 2 for the determination of carry-over
FSS-Lake 100 ppm	≥ 4 g	≥ 400 g
F-Lake 100 ppm	≥ 40 g	≥ 4,000 g
FSS-Lake 10 ppm	≥ 50 g	≥ 5,000 g

Table 2:

A laboratory must be available where microtracer analyses can be done. Appointments should be made in good time with this laboratory for analyses to be carried soon after the samples are taken.

5. COMPANY DETAILS REQUIRED

The following will be requested in advance from a compound feed company at which a control procedure is to be carried out:

a. a block diagram of the production installation in which it can be indicated during the implementation where the microtracer mix has been added and where samples are taken.

The following will be requested during the implementation of the control procedure:

b. the computer prints or copies of them which show:
   1. the composition of the feed mix
   2. the batch weight requested by the computer, and
   3. the actual batch weight

   or, if there is no computerisation:
   4. the composition of the feed mix
   5. the calculated batch weight This weight is obtained by adding the weights of the components
   6. the read-out of the actual batch weight.

The following will be requested to be able to calculate the batch weight for the mixer and the grain press:

c. where and how much molasses, vinasse and other liquid ingredients added to the main flow of the feed, and
d. where and how much fats, etc., are added to the main flow. The requested addition points are shown in the block diagram.

6. ADDITION OF THE MICROTRACER MIX

The microtrace mix (see section 2) is added to the first batch. The place where the microtrace mix is added depends on the carry-over path to be measured (see 7.1). The place where the addition of the microtrace mix must be done should be indicated in the block diagram for the production plant.
The place where the addition of the microtrace mix must be done should be indicated in the block diagram for the production plant. The batch weight requested by the process computer may be assumed.

7. TAKING AND HANDLING SAMPLES

7.1 Analysis samples

7.1.1 Taking the samples

During the implementation of the control procedure in a compound feed company samples are taken at locations agreed in advance:

a. after the mixer but as close as possible to the mixer (see section 13.1)
b. from the entrance to the finished product silo in the event of meal production or a pressed meal silo
c. from the entrance to the finished product silo in the event of grain production
d. another desired end point for the determination of the relevant carry-over path

If the meal or grain flow is not reachable at the desired locations then suitable openings should be made in consultation with the company.

Twenty samples are taken each time per sampling point. The statistical certainty is increased through the rise in the number of samples. The increase in the number of samples from 30 to 40 is, however, voluntary.

Meal production

From the first batch 20 samples of meal (immediately after the mixer) and 20 samples of meal (from the input to the finished product silo) are taken for the microtracer analysis (the sample quantity to be taken, see table 2).

From the second batch 20 samples of meal (immediately after the mixer) and 20 samples of grain (from the input to the finished product silo) are taken for the microtracer analysis (the sample quantity to be taken, see table 2).

Grain production

From the first batch 20 samples of meal (immediately after the mixer) and 20 samples of grain (from the input to the finished product silo) are taken for the microtracer analysis.

From the second batch of feed 20 samples of meal (immediately after the mixer) and 20 samples of grain (from the input to the finished product silo) are taken for the microtracer analysis (the sample quantity to be taken, see table 2).

If a split is desired with respect to the carry-over by the dosage/grinding/mixing line on the one hand and the press line on the other hand then during the first and second batches another 20 samples of meal for microtracer determination should be taken at the input to the pressed meal silo. The method of working is identical to the method for meal production.

Sample bags

All sample bags are provided with a sample code before the start of the production of the first batch of feed. The sample bags must be filled up to the edge and sealed air-tight to avoid de-mixing (in the case of meal samples) as much as possible.

Sampling

a. Production batch: Once the meal and/or grains flow starts for the batch to be inspected then 20 samples of meal and 20 samples of grains are taken spread as well as possible over the duration of the batch.

b. Production batch: Due to the irregular distribution to be expected of the microtracer particles in the carry-over batch (in the beginning very high numbers of microtracer particles and at the end very low numbers of microtracer particles) the sampling is done in a different way. The first three samples are continuously collected in a large collection container. The first sample represents the sampling time from 0 to 0.5 min, the second sample 0.5 to 1.0 minutes and the third sample 1.0 to 1.5 minutes in the feed flow. A sample is taken from each of these three collection samples via sampling splitting (quartering method). The other samples are taken as random samples every 0.5 minutes. For a total duration of the feed of 10 minutes there will be 20 samples collected of which the first three are collective samples and the other 17 are individual samples. For lesser durations the sampling intervals must be modified accordingly.

N. B.: It is very important that the samples are taken spread as well as possible over the duration of the batch in connection with the samples being representative of the batch as a whole.

7.1.2 Preparation of the samples

Each meal and grain sample is ground in a suitable grinder.

First grind the samples of meal and grain from the second batch (carry-over batch) and then those from the first batch. This ensures that the samples are ground in ascending sequence of their microtracer level.

Clean the grinder after each sample using compressed air.

Clean the grinder after each group of 20 samples using both compressed air and, after disassembly of the relevant parts, by brushing clean with a brush which is not too soft. There may be no carry-over of material from the previous group of samples.

Homogenise each grinding as much as possible and then place it back in the original bag.

7.1.3 Storage of analysis samples

Analysis samples which will not be tested within a week of being taken should be stored dry.

7.2 Analysis of samples

The sample packaging may not be opened during this period (see 13.2).
Homogenise the mix to be inspected in the sample bag as much as possible by stirring it with a spoon or spatula.
A sample of the desired size is taken from the sample to be analysed and subjected to a microtracer analysis.

7.3 Archiving

The filters with the colour points from the individual microtracer particles must be archived. A minimum archiving period of 1 year is suitable. The filter sheets can, however, be retained for more than 10 years.

8. DETERMINATION OF THE MICROTRACER PARTICLES

The microtracer particles from a sample are isolated because of their magnetic properties by way of filtering through a rotary detector with a rotary magnet. Other magnetic particles are also filtered out at the same time. The identification of the microtracer particles takes place by way of a bonding colouring agent which causes a chromatographic effect (= colour point) on a filter sheet after treatment with a developer. In order to make the colour points visible the filter is dampened with the developer, the microtracer particles are transferred quantitatively to the filter sheet and the colour development is stopped by then laying the filter sheet on a heated plate.

Other magnetic particles do not develop colour points and are removed from the filter sheet with a brush. The colour points developed on the filter sheet are counted. The microtracer level is indicated as the number of particles per gram of sample.

9. PROCESSING OF THE RESULTS

9.1 Non-standard results

After the addition of the microtracer mix to the feed in the first batch the microtracer level in the first samples to be taken will be lower than in the subsequent samples. This is because of a degree of carry-over of bare feed from the feed batch prior to the batch with microtracer.

An opposite effect is seen in the samples from the second batch of feed. Now the first samples show a relatively high microtracer level as a result of carry-over of feed containing microtracer from the second to the third batch. Normally the spread of the microtracer levels in the samples from the third batch is considerably more distorted than in the second batch. There is also no calculation of a probability for homogeneity and it is enough to make a graph of the average microtracer level per sample against the sample number. In as far as the samples are properly representative for the whole batch which means they have been properly spread over the total duration, the average carry-over of microtracer can be calculated as a percentage of the microtracer level in batch one.

9.2 The carry-over

The carry-over for the installation is calculated as follows in accordance with this control procedure per measurement point.
The average microtracer level of the analysis samples from the second batch divided by the average microtracer level on the basis of dry matter from the analysis samples from the second batch. By multiplying this figure by 100 the average carry-over percentage can be calculated.

9.3 The test for homogeneity

The following statistical data will be determined for the evaluation:

a. average number of particles
b. standard deviation for the number of particles
c. $\chi 2$ (chi squared) – value
d. Probability p in % as an indication of the homogeneity
e. Microtracer recovery percentage in %.

The probability is determined using the determined chi squared value and the number of degrees of freedom (see table 3). Values between 0.999 and < 0.0005 can be found. The assessment of the homogeneity is recorded by definition. The probability is calculated using an Excel table.

χ^2	1	2	3	4	5	6	7	8	9
1	.317	.607	.801	.910	.963	.986	.995	.998	.999
2	.157	.368	.572	.736	.849	.920	.960	.981	.991
3	.083	.223	.392	.558	.700	.809	.885	.934	.964
4	.046	.135	.261	.406	.549	.677	.780	.857	.911
5	.025	.082	.172	.287	.416	.544	.660	.758	.834
6	.014	.050	.112	.199	.306	.423	.540	.647	.740
7	.008	.030	.072	.136	.221	.321	.429	.537	.637
8	.005	.018	.046	.092	.156	.238	.333	.433	.534
9	.003	.011	.029	.061	.109	.174	.253	.342	.437
10	.002	.007	.019	.040	.075	.125	.189	.265	.350
11	.001	.004	.012	.027	.051	.088	.139	.202	.276
12	.001	.002	.007	.017	.035	.062	.101	.151	.213
13	**	.002	.005	.011	.023	.043	.072	.112	.163
14	**	.001	.003	.007	.016	.030	.051	.082	.122
15	**	.001	.002	.005	.010	.020	.036	.059	.091

Table 3: Table for the determination of probability, horizontal: number of degrees of freedom, vertical: chi squared values

10. REPORTING

The following is reported for each group of feed samples:

a. For the calculation of the homogeneity of the first batch of compound feed, the average number of microtracer particles in whole numbers
b. For the calculation of the homogeneity of the first batch of compound feed, the number of degrees of freedom of the system Number of analysed samples n-1
c. for the calculation of the homogeneity in the first batch of compound feed, the chi squared value (calculated from the empiric coefficient of variation for the analysed samples times the number of data divided by the average number of particles in the analysed samples)

d. from the number of degrees of freedom and the chi squared value, the probability as a percentage of the analysed samples [[(Chivert (chi squared; degree of freedom) × 100] × 100]
e. the calculated recovery percentage of the microtracer particles in the first batch of feed in relation to the number of microtracer particles in the added microtracer mix
f. The calculated carry-over in the installation from the number of microtracer particles in the second batch of feed in relation to the number of microtrace particles in the first batch

11. ASSESSMENT OF THE RESULTS

Homogeneity of the material

The calculated probability as a percentage is a measure for the homogeneity of the meal mix or grains in question from which the samples were taken. The probability indicates how probable it is that the tested sampled corresponds to a perfect mix.

If the value found in the test is identical with a probability of more than 5 % (0.05) then it may be assumed on the basis of the probability calculation that there is a "perfect mix".
If the value found in the test is identical with a probability of between 1% and 5% (0.01 to 0.05) then it may be assumed on the basis of the probability calculation that there is a "probable significant deviation from a perfect mix". This refers to a borderline case about which no unambiguous statement can be made. The test must be repeated.
If the value found in the test is identical with a probability of less than 1% then it may be assumed on the basis of the probability calculation that there is a "probable significant deviation from a perfect mix".
A key feature of the poisson distribution is that when there is a "perfect mix" the standard deviation of a test series must be (on average) equal to the square root of the average.

Two examples follow of the calculation of a homogenous and a non-homogenous mix.

Example 1: Homogeneous mix

Sample number	Number of particles counted, x	Average m	Difference x_n-d_n	Square of difference d_n^2
1	47	50	3	9
2	53	50	3	9
3	45	50	5	25
4	55	50	5	25
5	50	50	0	0
Average x=50			Sum d_n^2=S=68	

Table 4: Example of the calculation for a homogenous mix

Number of samples: n=5
Chi squared value χ^2: S: x = 1 (68: 50 = 1.4)
Table values from table 3:
horizontal: n – 1 = 4
vertical: 1
calculated probability: 0.910
calculated probability in %: 91.0%

Result: The calculated probability is greater than 5 %; there is therefore a homogenous mix.

Example 2: Non-homogenous mix

Sample number	Number of particles counted, x	Average m	Difference x_n-d_n	Square of difference d_n^2
1	43	53	10	100
2	57	53	4	16
3	70	53	17	289
4	35	53	18	324
5	61	53	8	64
Average x=53			Sum d_n^2=S=793	

Table 5: Example of the calculation for a non-homogenous mix

Number of samples: n=5
Chi squared value χ^2: S: x = 15 (793: 53 = 15)
Table values from table 3:
horizontal: n – 1 = 4
vertical: 15
calculated probability: 0.005
calculated probability in %: 0.5%

Result: The calculated probability is less than 1 %; there is therefore a non-homogenous mix.

12. NOTES

12.1 First sampling point

A feed mix is not homogenous after the dosage of the various components. Even after the grinding of the raw materials in the hammer mill this is only partly the case. Often finer raw materials are led around the hammer mill and carried straight to the mixer. A homogenous feed mix may therefore only be expected for the first time in the mixer. Taking samples directly from the mixer is difficult and may be dangerous and is certainly not recommended. The sampling should therefore be done after the mixer. In most companies this will be the outflow of the bunker under the mixer.

12.2 Storage of the samples

Samples which can not be examined in the short term should be stored in a dry area to retain sufficient free-flow for the test.

13. SAFETY

The control procedure is usually carried out in practice in a compound feed company.

For those who carry out the control procedure in a compound feed company the following safety rules apply:

a. the operatives will make themselves aware before the start of the work of the safety instructions which apply in the compound feed company
b. during their stay in the compound feed company the operatives are bound to follow the safety instructions of the compound feed company

14. PROCESSING OF COMPOUND FEED CONTAINING MICROTRACER

No special instructions.

15. LITERATURE

1. The use of Microtracers to determine Completeness of Mix
The use of microtracers for the determination of the homogeneity of mixes
David A. Eisenberg, President of Micro Tracers, Inc. of San Francisco

2. Mix with Confidence
Safe mixing
David A. Eisenberg, President of Micro Tracers, Inc. of San Francisco
International Milling Flour&Feed, June 1994

5.8 Control procedure for the measurement of carry-over using micro-tracers by weighing

1. FIELD OF APPLICATION
See 5.7 Control procedure for the measurement of carry-over using microtracers

2. DEFINITIONS
Production plant: A production plant is an installation which is suitable for the preparation of compound feeds.

Microtracer mix: For the testing of a compound feed the microtrace mix contains 4 kg feed lime or wheat grits and 500 g microtracer. Therefore 500 g microtracer is mixed with 1 ton of compound feed, which corresponds to a mixing accuracy of 1: 2000.

3. PRINCIPLE
Use will be made for the measuring substance of the so-called RF microtracer (elementary iron particles). With an average number of particles of 1,000,000 per gram. For the microtracer particles it is a case of particle distribution; the average number of particles varies depending on the microtracer batch. In order to determine the number of particles in question in the test a microtracer mix is produced in which the average number of particles is determined exactly for the microtracer used.

The number of particles of microtracer in the samples which were taken is determined by separating the microtracer particles from the other feed particles using a rotary detector. The sample should be led twice over the rotary detector for this.

Once the sample has passed the magnet then the excess product is brushed from the filter with a brush, do this accurately and with a rotating magnet.
Remove the filter from the magnet and transfer and return the microtracer in a tared copper weighing boat.

NB 1: In order to correct for “factory iron” at least three blank samples will be measured. In the final calculation there should be a correction for the average of the blank measurements.

NB 2: When adding the microtracer mix there should be 500 gram/ ton added. The sample size should be 300-500 grams.

4. EQUIPMENT AND TOOLS
See 5.7 Control procedure for the measurement of carry-over using microtracers

5. COMPANY DETAILS REQUIRED
See 5.7 Control procedure for the measurement of carry-over using microtracers

6. ADDITION OF THE MICROTRACER MIX
See 5.7 Control procedure for the measurement of carry-over using microtracers

7. TAKING AND HANDLING SAMPLES
See 5.7 Control procedure for the measurement of carry-over using microtracers

8. DETERMINATION OF THE MICROTRACER PARTICLES
By way of double filtration using a rotation detector with a rotary magnet the microtracer particles from a sample are isolated because of their magnetic properties. Other magnetic particles are also filtered out at the same time.
The identification of the microtracer particles is done by weighing.

NB 1: In order to correct for “factory iron” at least three blank samples will be measured. In the final calculation there should be a correction for the average of the blank measurements.
NB 2: When adding the microtracer mix there should be 500 gram/ ton added. The sample size should be 300-500 grams.

9. PROCESSING OF THE RESULTS
See section 5.7 Control procedure for the measurement of carry-over using microtracers

10 REPORTING
See section 5.7 Control procedure for the measurement of carry-over using microtracers

11. ASSESSMENT OF THE RESULTS
See section 5.7 Control procedure for the measurement of carry-over using microtracers

12. REMARKS
See section 5.7 Control procedure for the measurement of carry-over using microtracers

13. SAFETY
See section 5.7 Control procedure for the measurement of carry-over using microtracers

14. PROCESSING OF COMPOUND FEED CONTAINING MICROTRACER
See section 5.7 Control procedure for the measurement of carry-over using microtracers

5.9 Control procedure for the measurement of carry-over in animal feed preparation using methyl violet

This text will be added later

6 METHODS FOR MEASURING HOMOGENEITY OF DRY MIXTURES [2]

6.1 Introduction

The participant mixes feed materials, feed additives and veterinary medical products uniformly through the feed in accordance with the requirements in 6.7.1.2 in GMP+ B1 *Production, Trade and Services.* Measurement of the homogeneity of mixtures is in accordance with the protocols, which are laid down in this part of the appendix.

6.2 Frequency

A homogeneity test must be performed on each mixing installation. This test must done at least,

- At first use of the installation.
- At every significant change to the installation.
- Every 4 years.

6.3 Measurement of homogeneity

6.3.1 General

The measurement of homogeneity is statistically determined, by making use of direct or indirect methods.

6.3.2 Direct methods

Direct methods for measuring homogeneity are based on the **counting of particles**. So called microtracers are used as a measuring substance. Two different microtracers are suitable for the homogeneity analysis: Microtracer F and Microtracer FSS. Application of these methods lead to analysis results, which are analyzed as Poisson distributions. Homogeneity is expressed in terms of probability (p). The application of these methods must be in accordance with the description of the method in chapter 5 above.

[2] Dry compound feed or dry premixtures. Mixtures of liquid feed, emulsions, suspensions are out of scope.

Guidance

Example of the calculation of homogeneity with the direct Microtracer FSS method.
Dosage of Microtracer FSS is 10 g per ton of test mix

Homogeneity Batch	100 % filling dry, 50 Hz
Planned batch size:	5392
Overweight:	120
Real batch size:	5512
Addition of Microtracer Premix:	directly through an opening in the mixer on top of the mix
Time for emptying of pre-bin to mixer:	15 s
Dry Mixing Time:	90 s
Addition of Liquids:	0 s
Wet mixing time:	0 s
Total mixing time:	105 s
Sampling place:	after reddler before elevator
Number of Samples:	22
Sample Assayed, g:	20
Tracer Color:	FSS-red lake
Tracer Used per Metric Ton, g:	9,78

Analytical results:

Sample No.	Sampling time [s]	Microtracer Particle Count	Sample Assayed [g]	Corrected Particle Count
1	0	74	19,46	76
2	10	102	21,50	95
3	20	92	21,29	86
4	30	97	21,59	90
5	40	97	21,27	91
6	50	92	20,54	90
7	60	103	21,01	98
8	70	92	20,69	89
9	80	100	21,06	95
10	90	87	21,01	83
11	100	77	20,94	74
12	110	85	21,11	81
13	120	95	20,01	95
14	130	83	19,97	83
15	140	83	21,97	76
16	150	88	20,30	87
17	160	85	20,68	82
18	170	82	20,67	79
19	180	83	20,02	83
20	190	73	19,97	73
22	210	82	20,09	82
24	230	82	20,05	82

Statistical Evaluation:

Number of Data	22
Degrees of Freedom	21
Mean, Particles	85
Standard Deviation, +/- Particles	7
c^2 Chi-square =	13,02
Probability, %	**91**
Tracer Recovery, % =	104

Mixing uniformity:
Mixing is excellent.

Table 1: Definitions for Mixing Uniformity

	direct tracer	indirect tracer
	Microtracer	example: Manganese
	Probability p	Coefficient of Variation cv
Mixing is excellent	> 25 %	< 5 %
Mixing is good	> 5 % - < 25 %	> 5 % - < 8 %
Mixing is acceptable	> 1 % - < 5 %	> 8 % - < 12 %
Mixing is incomplete	< 1 %	> 12 %

6.3.3 Indirect methods

Indirect methods for measuring homogeneity are based on the **determination of a concentration of a substance** (Microtracer RF Lake Blue, cobalt, or additive). Indirect methods are:

- Method with tracer Microtracer RF Lake Blue
- Method with cobalt
- Method with tracer composed of an additive (Salinomycin)
- Method with a mix of manganese oxide and a protein-rich and a protein-poor mix

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 application of the above indirect methods must be in accordance with the descriptions in chapter 5.

6.4 Interpretation of homogeneity results

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

In case the homogeneity of the mixture is assessed as insufficient, the GMP+ participant must:

- Report on the probable cause(s)
- Carry out corrective measures
- Perform a new homogeneity test in order to verify that the measures taken lead to a good homogeneity.

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