

Differences between generic and Brand Specific Approved (BSA) anticoccidials

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Different maduramicin 1%-premixes were compared for evaluation of quality. Anticoccidial premixes consist of two elements: active compound and carrier. Eleven generic premixes originating from different countries were compared with Cygro®, the only EU BSA-approved maduramicin. Maduramicin concentrations were analysed and compared. Only Cygro® contained the claimed concentration. One generic had lower concentration than claimed (0.75%); all the other generics had at least 10% more active than claimed. Underdosing anticoccidials can cause poor control of coccidiosis, higher oocyst output and has been suggested to induce resistance faster. Overdosing maduramicin can cause target animal safety problems.

Premix quality was evaluated, using laser diffraction equipment, for parameters that impact homogeneity and thus imply a risk for under- or overdosing. Next to Cygro®, only three out of eleven generics had good results for premix features. Combined with active evaluation, just one generic would have passed release specifications of Cygro®. Another batch of this generic had excessive maduramicin content and poor particle strength.

As a conclusion, these results confirm the need for high requirements for anticoccidial premix registrations such as BSA in the EU. Generic premixes might cause significant problems during (poor parasitological control, toxicity) and after use (higher infection pressure, faster resistance).

Keywords: maduramicin; BSA; generic; anticoccidial

Introduction

Anticoccidials are premixes added to the ration of chickens and turkeys to overcome the impact of *Eimeria* spp., ubiquitous apicomplexan parasites. In the European Union (EU), these premixes are currently registered as feed additives under Regulation (EC) no 1831/2003, also called 'Brand Specific Approval' (BSA) anticoccidials. This Regulation was implemented in order to regulate the registration of this class of feed additives, with the ultimate goal to improve the safety of these products for animals and consumers. An important feature of this Regulation is that data, generated to achieve a registration under BSA, are linked to a commercial formulation (OJ, 2003).

Next to quantitative and qualitative characteristics of the active ingredient, also the formulation is a crucial element of a premix, with regards to usability in commercial conditions (homogeneity of mixing and loss of product after handling), safety of the product for animal (overdosing) and consumer (residues), and efficacy on the short (concentration active ingredient) and long term (resistance development).

Poultry producers outside EU are very often approached by companies marketing generic copies of these BSA approved anticoccidials, and have questions whether these generics can be considered as valid alternatives for the BSA products.

In this series of experiments, an attempt was made to compare the quality of maduramicin premixes registered under BSA and generic premixes available outside EU. Maduramicin 1% premix Cygro® is registered with an inclusion rate of 500 gram per ton of final feed, resulting in a maduramicin dose of 5 gram per ton or 5 parts per million (ppm) in the final feed.

Materials and Methods

The trials were run with maduramicin 1% generic premixes produced in different countries, including Israel, Bulgaria, Egypt and China. At least two kilograms of the premixes were sent, preferably in the original packaging, to the laboratory. After first gently shaking the premix samples, they were split in three sub samples for further analysis at specialized laboratories. A first sample was sent for scanning electron microscopy (SEM) to the Department of Morphology (faculty of Veterinary Medicine, Ghent University, Belgium) to allow a visual inspection of the premixes. A second sample was sent for analyses of the active ingredient concentration at a Beltest-accredited laboratory, specialized in analysis of feed samples (Lavetan, Belgium). The third sample was sent to the Department of Applied Analytical and Physical Chemistry (Ghent University, Ghent, Belgium) for evaluation of particle size distribution of the premix by using a laser diffraction technique (Malvern Mastersizer S®, equipped with MSX-64 dry powder feeder). From the volume-weighted particle size distribution, different parameters, such as the fraction of particles smaller than 50 µm (indicating the fraction of the premix that is considered as dust), the distribution span, the number of modes, the modal diameter(s), and the Sauter Mean Diameter (smd, D32), were calculated. The latter is the diameter of a hypothetical spherical particle of which the ratio of surface area to volume is equal to that of the sample (Allen, 1999). This set of parameters that characterize the particle size distribution was measured under two different pressure conditions (at 0.6 bar and at 3.0 bar) for the venturi system that dispersed the dry powder into a stream of compressed air. Changes in the particle size distribution when measured under different pressure conditions indicate that the particles are not able to sustain physical stress and are an indicator of poor particle strength (Chen & Lloyd, 1994).

Results and discussion

The results for the active concentration of maduramicin are given in *Table 1*.

Table 1: Concentration of maduramicin in different 1% BSA and generic premixes

Sample	Expected concentration	Measured concentration	Origin of sample
CYGRO®	1%	1,00%	EU
GEN A	1%	1,30%	Israel
GEN B	1%	1,20%	Bulgaria
GEN C	1%	1,20%	Egypt
GEN D 1	1%	1,10%	Egypt
GEN D 2	1%	1,20%	Egypt
GEN E 1	1%	1,10%	Egypt
GEN E 2	1%	1,30%	Egypt
GEN E 3	1%	1,10%	Egypt
GEN F	1%	1,30%	China
GEN G	1%	0,75%	Egypt
GEN H	1%	1,20%	Egypt

From *Table 1*, it was concluded that only 3 of the tested premixes were within the specifications for the active ingredient maduramicin ammonium (0.95-1.11%) of the BSA reference product Cygro®. One of the generics, in *Table 1* GEN G, contained a too low maduramicin concentration. Too low concentrations of the active obviously could lead to insufficient coccidial control. Depending on the coccidial challenge present in the field, this could lead to clinical coccidiosis and/or subclinical coccidiosis. The latter, although not easy to diagnose, is expected to be related to higher incidences of bacterial enteritis. As faster resistance towards anticoccidials has been related to too low inclusion levels of drugs (De Gussem, 2005), the long term consequences might be even more detrimental. Even in low coccidial challenge, when no signs of clinical coccidiosis are evidenced, resistance towards maduramicin is therefore expected to be developed substantially faster.

Most of the generics included in this survey, contain levels of maduramicin higher than expected. Also too high levels of maduramicin are extremely undesirable: the tolerance studies as performed with the original BSA approved product indicate negative impact on performance starting from 8 ppm. When

considering an excess concentration of 30% of maduramicin and dosing at the recommended 500 grams per ton, one would expect that birds treated with this premix would receive 6.25 ppm maduramicin, still below this threshold of 8 ppm. Unfortunately, this does not reflect the practical field conditions with well known variations in feed consumption of the individual birds, and even more importantly the segregation of the active, as will be explained further in the text. The level of segregation is formulation-dependant. All BSA data demonstrating the safety and efficacy of maduramicin originate from trials performed with the specific Cygro® formulation. Therefore, these data can not be used to demonstrate the safety and efficacy of other maduramicin formulations. To have an idea of the comparability of the generic formulations with Cygro®, a second set of experiments was performed.

Table 2: Particle size distribution information of different premixes. Products are coded differently from Table 1.

Sample	Measurements at 0.6 bar							Measurements at 3.0 bar	
	D32 (µm)	% < 50 µm	Span	# modes	mode 1 (µm)	mode 2 (µm)	% mode 1	D32 (µm)	Fragility (%)
CYGRO	503,5	0	0,92	1	585,9	---	100	501,2	0,5
GEN A 1	298,1	0,6	1,38	1	439,1	---	100	263,4	11,6
GEN A 2	280,6	0,8	1,27	1	444,0	---	100	205,1	26,9
GEN B	688,5	0,2	0,96	2	852,6	70,0	99	794,0	-15,3
GEN C	477,2	0,4	1,10	1	626,8	---	100	475,0	0,5
GEN D	554,5	0,0	0,82	1	602,9	---	100	514,9	7,1
GEN E	7,2	88,3	5,78	2	9,5	316,3	92	5,6	21,3
GEN F	9,1	57,5	6,45	3	28,4	196,4	57	4,0	56,1
GEN G 1	12,4	56,4	5,95	2	22,8	164,3	63	13,2	-5,8
GEN G 2	5,3	77,1	13,14	2	10,5	255,8	88	3,8	28,2
GEN G 3	22,3	48,2	4,61	2	153,2	20,7	55	16,3	26,7
GEN H	12,2	90,7	2,21	1	26,6	---	100	9,0	26,8

From Table 2, it can be derived that the BSA product Cygro® had an smd of 503.5 µm. This is a particle size suited for a premix intended for use in poultry rations, at an inclusion rate of 5 ppm. Particles larger relative to the feed mash will tend to rise when mixed in the feed (Williams, 1973), smaller particles will percolate. Generics E, F, G1, G2, G3 and H consisted of particles smaller than 50 µm. Products consisting only of particles smaller than 50 µm are considered in the feed mill industry as being powders and are recognized as not useable since too much of the product will be lost during mixing and transport of the feed. Depending on the feed type, segregation will occur and different parts of the feed will contain substantially higher or lower concentrations of active (Thomas, 2003), in this case maduramicin. None of these premixes therefore can be considered as equivalent to the BSA registered product, and a higher or lower intake of the active can be expected, especially when the active concentration of the premix before handling is not within the specifications, as demonstrated in the first analysis experiment. The other generics and Cygro® proved to have no or only a limited amount of dust particles. The span gives an indication on how much variation there is in the particle size distribution since it corresponds to the difference between the diameters corresponding to a cumulative volume of 90 and 10%, respectively, divided by the median diameter (corresponding to a cumulative volume of 50%): the lower the span, the more homogenous the particle size distribution is. On the condition of course that the particles have the right size, a low span will result in more homogenous mixing. The number of modes indicates whether there are subpopulations of different particle size in the sample or not. For instance, simple mixed premixes, where the active is combined with a filler material, will have two modes. A typical example is GEN B from Table 2. Here the filler is represented by the main mode at 852,6 µm (99% of the particles) whereas the active is represented by a second minor mode at 70 µm (1% of the particles). Only the characteristics of mode 2 (active) will be relevant, as from the moment the premix is mixed with the feed, the filler will have no value

anymore for the mixing and segregation characteristics of the active. With a particle size of 70 μm , percolation will cause the active to segregate. Products with only one mode are considered as a valid active/carrier combination, where the mixing and segregation properties of the carrier will help the active to be homogeneously distributed through the feed. These differences in composition of the premixes were also shown by the SEM photos taken from the different premixes. Figure 1, 2 and 3, represent SEM photos of Cygro®, GEN F and GEN G3, respectively. The Cygro® particles proved to be very uniform, without small dust particles. GEN F was one of the premixes being considered as a powder, and GEN G3 is one of the generic samples showing a lot of variation in the particle sizes.

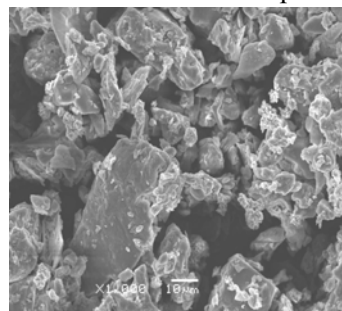
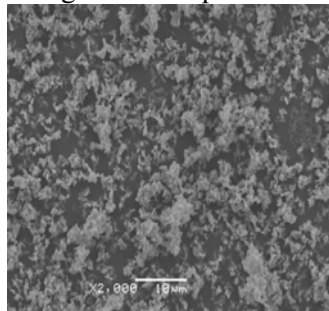
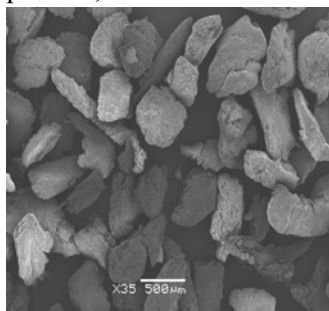


Figure 1. SEM picture of Cygro® Figure 2. SEM picture of GEN F Figure 3. SEM picture of GEN G3

Another important parameter is the durability of the particles. Particles that break under physical stress, for instance during mixing or transport, into smaller particles will show a considerably lower D32 at higher dispersing air pressure, and this is expressed as the fragility, which is defined as the complement of the ratio of the smd obtained at 3.0 and 0.6 bar, respectively. A low fragility indicates strong particles, resistant to a certain level of physical stress. The Cygro® formulation performed very well (0.5%) in this test, as did generic C. The other generics had a higher fragility which will result in altered mixing properties. In addition, by breaking up or wearing off the granules, the active can get detached from the carrier, resulting in the loss of function of the carrier. Overall, three out of eleven generics showed premix characteristics equivalent to the BSA registered product. The usability of the other generics in feed mills is contraindicated.

As a conclusion, from the eleven generics in this survey, only one showed both for active concentration and premix characteristics features equivalent to the BSA registered product. The other batch of this same generic product did not have these acceptable features and therefore the consistency of this producer should be questioned. Based upon this survey, generic maduramicin premixes do not guarantee safe and efficacious use of these anticoccidials. As intended in BSA regulation, Cygro® demonstrated all the features required to be used in a consistent, efficacious and safe way in feed mill operations around the world.

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