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Towards a future with zero medicinal zinc oxide

Lea Hübertz Birch Hansen, Ph.D. | Product Management, Swine
Animal & Plant Health & Nutrition, Chr. Hansen A/S

Upcoming ban of medicinal zinc oxide

Zinc oxide (ZnO) can be referred to as a veterinary medicinal product when supplemented in levels above 150 ppm. In several European countries, medicinal ZnO at levels of 2500 ppm is used for controlling the development of post-weaning diarrhea (PWD) in pigs. However, the European Medicines Agency has banned all authorizations for veterinary medicinal products containing zinc within all European member states starting June 2022 (European Medicines Agency, 2017). Thereby, the maximum level of zinc permitted in the feed cannot exceed 150 ppm. The decision to ban medicinal ZnO was made due to concerns about heavy metal accumulation in the environment and the potential for developing antimicrobial resistance. It is generally presumed that a removal of zinc from the post-weaning diet will lead to a substantial increase in the use of antibiotics for nursery pigs in Denmark. SEGES Pig Research Center estimated an increased cost of 4 DKK per pig (due to reduced performance and increased labor related to inspection and medicinal treatments) if no alternative is found (Kjeldsen *et al.*, 2017; SEGES, 2017). The ban was announced in June 2017, and ever since the pig industry has made a big effort to identify potential alternatives to medicinal ZnO.

Since veterinary regulation is country specific, medicinal ZnO has not been utilized to control PWD in all European countries. In the Netherlands for example, feed manufacturers have never been authorized to use medicinal ZnO in nursery diets. France, on the other hand, was only permitted to utilize medicinal ZnO in 2016, which is why very few pig producers have adopted it. In Germany, the ban of medicinal ZnO already became effective in June 2021. Therefore, the European countries affected by the ban are Denmark, Spain, Italy, UK and Poland. Outside of Europe, in UK, ZnO veterinary products released before June 26, 2022, and therefore in the supply chain and available for sale to feed compounders, can continue to be used until the end of the shelf life.

Why is medicinal zinc oxide challenging to replace?

Zinc is a very important trace element in pig nutrition due to its capability to ensure the activity of several enzymes involved in digestion, metabolism as well as cellular signaling and respiration. Consequences related to zinc deficiency are low appetite, growth retardation and impaired feed conversion rate. Even though the importance of zinc is well established, the precise mode of action has not yet been fully elucidated. Nevertheless, the main effect of zinc seems to be related to improved intestinal morphology and nutrient absorption (Bonetti *et al.*, 2021). Zinc has the potential to exert multiple beneficial effects on the host, which is why identifying a one to one replacement as efficient as zinc can be difficult.

Many strategies are being investigated in the search for an alternative to medicinal ZnO. Investigations of potential nutritional strategies led to the following alternatives: low protein diets, reducing buffering substances, water acidification, focus on sow feeding program, creep feed, and additives such as probiotics, prebiotics, and acids. Non-nutritional strategies being investigated are application of biosecurity standards, hygiene including cleaning and disinfection, vaccination programs and management improvements (climate, stocking density as well as water access and quality).

There is no one to one replacement of medicinal zinc oxide

Since the ban was announced in 2017, SEGES Danish Pig Research Center has initiated several studies investigating potential alternatives to medicinal ZnO. As part of the investigation, SEGES has investigated several Danish pig farms that are not using medicinal ZnO in order to identify consistent factors which potentially can be utilized by other farmers when they are forced to terminate the use of medicinal ZnO. The overall conclusion of these studies was that a successful weaning process without medicinal ZnO takes several initiatives. The main variables identified to be of importance for a successful weaning without medicinal ZnO were high hygiene, feed intake immediately after weaning (feeding on the floor or via temporary troughs), protein content and source, as well as extra water allocation (Weber *et al.*, 2019b, 2019a). Out of the 25 investigated farms (using no medicinal ZnO), the following protein sources occurred with the greatest frequency: Potato protein, soy protein concentrate, fish meal and milk powder (Poulsen and Weber, 2020).

SEGES has also investigated the impact of different probiotic solutions and found that none of them could replace medicinal ZnO (Kjeldsen *et al.*, 2017). In another study, prevalence of PWD was found to be reduced while performance tended to be enhanced when a specific concept was tested. The concept

included allocation of soaked feed 3-4 times per day one week pre- and post-weaning, optimized feed formulation with focus on protein level and sources as well as focus on reduced mixing of piglets at weaning (Sørensen and Krogsdahl, 2021). However, not all concepts have proven to be a success. In another study, four different feed formulation concepts were investigated. Only one of the concepts successfully replaced medicinal ZnO, yet even when considering the savings on antibiotics, the concept was not concluded to be of interest for the farmers due to an additional price of 1 euro per pig (Kjeldsen and Krogsdahl, 2018).

With a focus on feed ingredients, fiber sources have been studied, yet, neither wheat bran nor beet pulps included in the nursery diet at 5% but without medicinal ZnO influenced diarrhea prevalence or performance (Kjeldsen *et al.*, 2021). One of the widely investigated strategies for a future with zero medicinal ZnO is the reduction of crude protein in feed as well as focus on protein source.

According to SEGES, regardless of soy ingredient used, reducing crude protein with 10 grams of digestible protein per feed unit during the first two feed phases did not significantly reduce the prevalence of PWD. Only by reducing the protein content with 30 grams of digestible protein per feed unit during the first two feed phases prevalence of PWD could be significantly reduced, yet with the consequence of impaired performance (Kjeldsen *et al.*, 2020). In fact, SEGES concluded in another study that low protein strategies reducing the prevalence of PWD entail approximately 15 gram lower daily gain during the nursery period (6-30 kg) (Kjeldsen *et al.*, 2019).

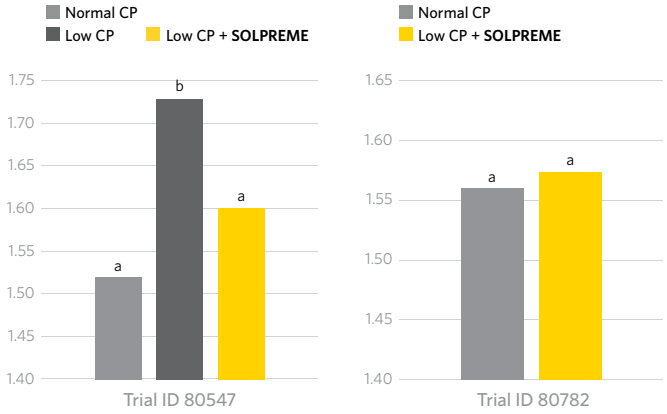
A probiotic combined approach should ensure return of investment

Eliminating medicinal ZnO from the nursery diet is not easy. It has been widely accepted that the future alternative to medicinal ZnO will comprise a combined approach. The challenge will then be to formulate the feed to have significant beneficial impact on PWD without compromising the return of investment, whether that will be through impaired performance or too high investment costs.

Two recent studies have investigated the effect of including the probiotic product **SOLPREME®** in a low protein pre-starter nursery diet on PWD and performance (Internal trial ID 80547 and 80782). Both studies found that the combination of **SOLPREME** and a low protein pre-starter nursery diet prevented the expected impairment of performance (Figure 1), while reducing the number of days with diarrhea post-weaning (Figure 2).

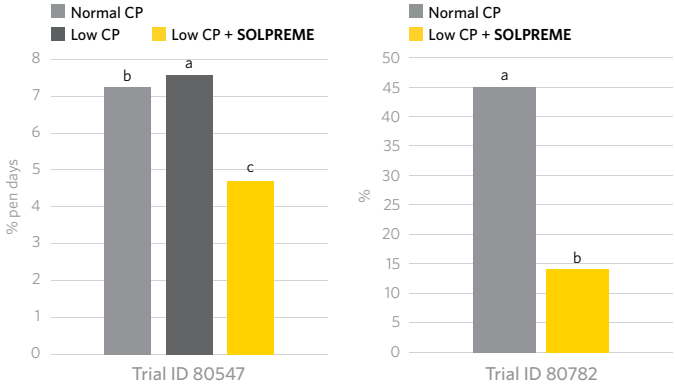
Interestingly, reducing the protein content in the pre-starter diet of trial 80547 did not have beneficial impact on prevalence of diarrhea, however it still impaired performance. This may be in agreement with Kjeldsen *et al.* (2020), who concluded that a certain reduction of protein is needed to control PWD. Nevertheless, adding **SOLPREME** to the low protein diet significantly reduced the prevalence of diarrhea.

Figure 1. Feed conversion ratio during the first two weeks post-weaning in two trials investigating the effect of low crude protein (CP) and **SOLPREME** application in pre-starter nursery diets. Values lacking a common letter are significantly different ($P \leq 0.05$).



SOLPREME has been proven to increase the activity of enzymes, thus leading to a higher utilization of protein in feed. The capability of **SOLPREME** probiotics to increase the availability of protein is most likely the contributory cause leading to sustained performance in weaned piglets fed a low protein pre-starter diet. Furthermore, the two **SOLPREME** strains were selected for their capacity to inhibit *E. coli* F4 and F18. Beside their direct inhibition of *E. coli*, both *in vitro* and *in vivo* studies have demonstrated **SOLPREME** improving intestinal integrity as well as beneficially modulated the gut microbiota and immune system. Consequently, the multiple probiotic mechanisms combined with a low protein pre-starter diet are driving the reduction in diarrhea prevalence.

Figure 2. Percent pen days with soft and liquid fecal consistency during the first two weeks post-weaning in two trials investigating the effect of low crude protein (CP) and **SOLPREME** probiotic application in pre-starter nursery diets. Values lacking a common letter are significantly different ($P \leq 0.05$)



When utilizing this approach, the investment in the probiotic will reduce the prevalence of PWD as well as costs related to treatment, and possible impaired performance of sick pigs can be avoided. In addition, the investment will be compensated by the reduction in feed costs due to the lower protein content. Including **SOLPREME** in a low protein pre-starter nursery diet is therefore a promising strategy supporting a healthy weaning in a future with no medicinal ZnO.

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