

#114

**Effectiveness of Anthelmintics:
Specific Recommendations for Chickens
*Gallus gallus***

VICH GL21

Guidance for Industry

Draft Guidance

This guidance document is being distributed for comment purposes only.

This version of the guidance replaces the version made available June 2002. This revision clarifies the definition of adequate infection in individual animals, updates considerations for field studies, and makes additional clarifying changes.

Submit comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with docket number FDA-2022-D-1494.

For further information regarding this document, contact Aimée Phillippi-Taylor, Center for Veterinary Medicine (HFV-114), Food and Drug Administration, 7500 Standish Place, Rockville MD 20855, 240-402-0601, email: <mailto:aimee.phillippi-taylor@fda.hhs.gov>.

Additional copies of this draft guidance document may be requested from the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville MD 20855, and may be viewed on the Internet at <https://www.fda.gov/animal-veterinary>, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>, or <http://www.regulations.gov>.

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International Cooperation on Harmonisation of Technical Requirements
for Registration of Veterinary Medicinal Products

VICH GL21 (ANTHELMINTICS: CHICKENS – GALLUS GALLUS)

May 2022

Revision at Step 9

For consultation at Step 4

Efficacy OF ANTHELMINTICS: SPECIFIC RECOMMENDATIONS FOR CHICKENS – GALLUS GALLUS (REVISION 1)

Revision at Step 9
Recommended for Consultation at Step 4 of the VICH Process
in May 2022
by the VICH Steering Committee

This Guidance has been developed by the appropriate VICH Expert Working Group will be subject to consultation by the parties, in accordance with the VICH Process. At Step 7 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

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I. Introduction

The present guidance for chickens was developed by the the Working Group established by the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medical Products (VICH), Anthelmintic Guidances, and subsequently revised in 2022. It should be read in conjunction with Guidance for Industry (GFI) #90 (VICH GL7), “Effectiveness of Anthelmintics: General Recommendations,”¹ which should be referred to for discussion of broad aspects for providing pivotal data to demonstrate product anthelmintic effectiveness. The present document is structured similarly to GFI #90/VICH GL7 with the aim of simplicity for readers comparing both documents.

The aim of the guidance for chickens is: (1) to be more specific for certain specific issues for chickens not discussed in GFI #90/VICH GL7; (2) to highlight differences with GIF #90/VICH GL7 on effectiveness data recommendations; and (3) to give explanations for disparities with GFI #90/VICH GL7. We recommend that sponsors refer to the pertinent procedures described in detail in other published documents, e.g., World Association for the Advancement of Veterinary Parasitology (WAAVP) guidelines for evaluating the efficacy of anthelmintics in chickens and turkeys. *Veterinary Parasitology* 116: 159-173, 2003, and updated versions as they are published. For other poultry, the principles outlined in this guideline should be used where applicable.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA’s guidance documents should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

¹ <https://www.fda.gov/media/70349/download>

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A. General Elements

1. The Evaluation of Effectiveness Data

Only controlled tests based on parasite counts of adults/larvae should be acceptable both for the dose determination and dose confirmation studies, since critical tests generally are not considered to be reliable for chickens. Egg counts with identification of the genus should be the preferred method to evaluate the effectiveness in field studies. Adequate parasite infection should be defined in the protocol according to regional prevalence or historic data and/or statistical analysis.

2. Use of Natural or Induced Infections

Dose determination studies generally should be conducted using induced infections with either laboratory strains or recent field isolates.

Dose confirmation studies should be conducted using naturally-infected birds which can have superimposed induced infections. This procedure should allow a wide range of parasites to be present in the experimental birds. Also, induced infections in one of the studies should be acceptable. Studies for larval stages should be conducted with induced infections.

The history of the parasites used in the induced infection studies should be included in the final report.

3. Number of Infective Parasitic Forms Recommended for Induced Infections

Table 1 indicates the number of eggs/cysticercoids recommended to be used and will depend on the isolate that is used. The final number of eggs/cysticercoids used in the infection should be included in the final report.

Table 1. Range of Infective Stages Recommended to Produce Adequate Infections in Chickens for Anthelmintic Evaluation

Parasite	Range
<i>Ascaridia galli</i>	200 – 500
<i>Capillaria obsignata</i>	100 – 300
<i>Heterakis gallinarum</i>	200 – 300
<i>Raillietina cesticillus</i>	50 – 100
<i>Syngamus trachea</i>	200 – 600

Some factors to consider for induced infections in chickens are:

- a. Young birds should be used in the studies;

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- b. To maximize the establishment of adequate infections, it is recommended to use low numbers of infective stages;
- c. Stress (e.g., poor diets) is not recommended to generate helminth infections; and
- d. Housing conditions should not allow accidental infections.

4. Recommendations for the Calculation of Effectiveness

4.1 Factors to Support a Claim

To support a claim the following pivotal data should be included:

- a. Two dose confirmation studies conducted with a minimum of six adequately infected experimental units (individual birds or pens, see section [II. Glossary](#)) in the non-medicated control group in each study. The infection of the experimental units in the study will be deemed adequate based on historical, parasitological, and/or statistical criteria;
- b. The differences in parasite counts between treated and control experimental units should be statistically significant ($p \leq 0.05$); and
- c. Percent effectiveness should be 90% or higher and calculated and interpreted using the procedures described in section A.4.2. *Calculation and Evaluation of Percent Effectiveness* of GFI #90/VICH GL7.

4.2 Number of Experimental Units (Dose Determination, Dose Confirmation, and Persistency Studies)

The minimum number of experimental units used per experimental group is a critical point. Although the number of experimental units will depend on the possibility to process the data statistically according to the adequate statistical analysis, it has been recommended, to achieve harmonization, that the inclusion of at least six experimental units in each experimental group is a minimum.

4.3 Adequacy of Infection

The minimum adequate number of helminths in individual control birds should be defined in the protocol. However, final conclusions regarding adequacy of infection will be made as part of the final report based on statistical analysis, historical data, literature review, or expert testimony. If the experimental unit is a pen, an adequately infected pen should be defined by a minimum number of adequately infected birds out of the total number of birds in that pen (i.e., percentage of adequately infected birds in the pen). The range of chicken helminths (adults) considered adequate to grant a claim will vary according to the species. Generally, a minimum of 20 *A. galli* in individual control birds is considered to be an adequate infection. Lower individual counts may be expected with *H. gallinarum*, *C. obsignata*, and *R. cesticellus*. Necropsies should be conducted within 10 days of treatment.

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4.4 Label Claims

Generally, for adult claims, the treatment should not be administered earlier than 28 days after infection. It is recommended to include at least six sentinel birds for helminth characterization and quantification before treatment is initiated. Generally, for L4 claims, treatments should be given 7 days after infection, except for *A. galli* and *H. gallinarum*, which should be 16 days after infection.

5. Treatment Procedures

The method of administration (oral, parenteral, topical, slow release, etc.), formulation, and extent of activity of a product will influence the protocol design.

When the drug is to be administered in the water or in a feed, it should be done as much as possible following the labeling recommendations. Palatability/consumption studies may be recommended for medicated feeds. Samples of medicated water or medicated feed should be collected to confirm drug concentration. The amount of medicated product provided to each animal should be recorded to ensure that the treatment satisfies the label recommendations.

6. Bird Selection, Allocation, and Handling

Test birds should be clinically healthy and representative of the age, sex, and class for which the claim of the test anthelmintic is to be made. In general, birds should be young and from a breed that is susceptible to helminth infections. If birds are housed in pens (e.g., cages or floor pens), the birds should be randomly assigned to each pen. The experimental units should also be randomly assigned to each treatment group. Randomization to treatment group should be performed using an adequate method that should be described in the protocol and final report. Blocking is only recommended if it is expected to reduce residual error in the study. If blocking is used, blocks should be included as a random effect in the statistical model. Nevertheless, blocking is not always the most appropriate method for reducing residual error. Alternative methods may therefore be considered, e.g., a suitably selected covariate.

Animal housing, feeding, and care should follow recommendations for welfare, including vaccination according to local practices. This information should be provided in the final report. A minimum 10-day acclimatization period is recommended. Housing and feed/water should be adequate according to the geographical location. Birds should be monitored daily to determine adverse reactions.

B. Specific Evaluation Studies

1. Dose Determination Studies

If the treatment recommends extended administration, one or more studies are recommended to determine the minimum treatment period for effectiveness.

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2. Dose Confirmation Studies

No species-specific recommendations.

3. Field Effectiveness Studies

Depending on the facilities available, the experimental unit may be the animal, pen, or the shed/house (see section [II. Glossary](#)). The design of the field studies should represent current commercial conditions and should be replicated in different geographic locations and in different production class(es), depending on the indication being pursued. Housing will differ based on the production class under investigation (e.g., layers vs. broilers). The protocol should state the number of experimental units per treatment group (sample size), describe allocation (proportion) to treatment groups, and include a brief description of how the sample size was determined. Regardless of whether one or multiple parasites are being evaluated within a study, an appropriate sample size calculation or justification is necessary prior to study conduct.

When commercial facilities (or similar) are used, the shed/house should be subdivided, when possible, to allow for sufficient replication to enable a statistical analysis. If the shed/house is the experimental unit and there is only one replicate per treatment group at a study site, the study may need to utilize additional sites with the same housing conditions to achieve sufficient replication and enable a statistical analysis. Otherwise, a study with one replicate can only be summarized using descriptive statistics and may not provide sufficient inferential value.

Effectiveness should be assessed by the reduction of worm counts in all birds or in representative birds as determined by comparing the treated and control groups. If representative birds are used for worm counts, the protocol should describe procedures for random selection of animals (number and percentage) to be necropsied. Fecal egg counts may be used to establish pre-treatment infection levels and parasite species present. A comparison of pre- and post-treatment fecal egg counts may be included but is not required. If fecal egg counts are evaluated, fresh, clean droppings should be collected immediately before treatment, and at 7 to 14 days after treatment. The fecal sampling method, number of pens/animals sampled, and egg counting technique should be defined in the protocol. Standard, well accepted techniques should be used and fully described in the protocol and final report.

Clinical observations, production variables, and records of culls and mortality should be maintained and compared to control birds and historical data of the commercial establishment. If birds are processed at the end of the study, slaughterhouse inspection reports with final observations regarding possible abnormalities, which are collected per the standard practices of the slaughterhouse, should be included in the final report. However, if the study duration does not coincide with or include slaughterhouse processing, these data are not required.

II. Glossary

EXPERIMENTAL UNIT: The entity (e.g., individual animal, cage, pen, or shed/house) which can be independently and randomly assigned to a treatment, and whose response to the assigned treatment can be independently evaluated. The experimental unit is the basic unit for the

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statistical analysis. The experimental unit may be the individual bird or the pen/shed/house, depending on the circumstances of the study.

- 1) The pen/shed/house is the experimental unit in the analysis if all birds in a pen/shed/house are provided the same treatment through medicated feed or water; or
- 2) The individual bird is the experimental unit in the analysis if the treatment can be individually administered, the treatments are randomly assigned to birds within a pen/shed/house, and the endpoint can be evaluated independently for each bird in a pen/shed/house.