CITIZEN PETITION

Submitted by Elanco Animal Health
May 28, 2020

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I. ACTIONS REQUESTED

Elanco Animal Health ("Elanco") respectfully submits this Citizen Petition to the U.S. Food and Drug Administration ("FDA") to request that the Agency take important steps with regard to its approval of generic versions of Elanco's Rumensin® (monensin) Type A medicated article.

Elanco is a global animal health company that develops products and knowledge services to prevent and treat disease in food animals and pets in more than 90 countries. Elanco discovered and developed Rumensin to improve the health and performance of beef and dairy cattle. Over the 45 years since Rumensin was first approved in the US, it has been widely adopted around the world and Elanco has conducted over 400 research studies to help global cattle producers adapt Rumensin to changing feeding programs and cattle management systems.

As detailed further below, Elanco is concerned that the recently approved Huvepharma Monovet® 90 ("Monovet") generic monensin Type A medicated article does not meet the requirements for bioequivalence required under section 512 of the Federal Food, Drug, and Cosmetic Act ("FDCA"). FDA's Center for Veterinary Medicine ("CVM") approved Monovet, even though Huvepharma's Abbreviated New Animal Drug Application ("ANADA") did not meet the requirements for establishing bioequivalence under section 512(n) of the FDCA, as clearly described in long-standing CVM guidance.[1] Instead, Huvepharma's claim of bioequivalence was based on a single clinical end-point study in beef cattle at a dose that is insufficiently sensitive to demonstrate bioequivalence, and an *in vitro* dissolution study in a non-bio-relevant media. A comparative dissolution study conducted by Elanco in bio-relevant media yielded very different results, further undermining any conclusions about the bioequivalence of Monovet to Rumensin.

Ultimately, the Monovet ANADA did not meet the bioequivalence requirements of section 512(n) of the FDCA, as described in long-standing CVM guidance, GFI #35, and therefore Monovet should not have been approved. The additional data generated from Elanco's comparative *in vitro* dissolution study underscores the fact that Monovet may not, in fact, be bioequivalent to Rumensin.

Accordingly, and as detailed herein, Elanco respectfully requests that FDA:

1. Commence withdrawal procedures for Huvepharma's ANADA for generic Monovet Type A medicated article for use in cattle and goats and all combination approvals as

[1] *FDA, CVM, GFI #35, Bioequivalence Guidance* (Nov. 2006) ("GFI #35").

required by section 512(e)(1) of the FDCA when new information reveals that the drug is not safe, or that there is a lack of substantial evidence of efficacy; and

2. Consistent with 21 C.F.R. § 10.115(d)(3), as well as the Administrative Procedure Act ("APA") and section 701(h) of the FDCA, refrain from approving future ANADAs for generic monensin Type A medicated articles and combination approvals *unless and until* either: (1) the ANADA includes at least two clinical end-point bioequivalence studies consistent with *FDA, CVM, GFI #35, Bioequivalence Guidance* (Nov. 2006) ("GFI #35"); or (2) CVM issues a new guidance document explaining an alternative approach to demonstrating bioequivalence.

Elanco strongly believes these steps are necessary to ensure the safety and efficacy of generic monensin Type A medicated articles and combination approvals, and to maintain the high standards required under section 512(n) of the FDCA for all such generic products.

II. STATEMENT OF GROUNDS

A. Background

Elanco developed and received approval for Rumensin® (monensin, USP) (NADA 095-735) based on studies demonstrating safety and efficacy. Rumensin is a Type A medicated article containing monensin. Approved claims for monensin for cattle under NADA 095-735 can be summarized as follows:

Calves: Coccidiosis control
Cattle fed in confinement for slaughter: Feed efficiency, Coccidiosis control
Growing cattle on pasture or in dry lot: Weight gain, Coccidiosis control
Mature reproducing beef cows: Feed efficiency, Coccidiosis control
Dairy cows: Milk production efficiency

The sites of action for monensin are: (1) the gastrointestinal tract, for coccidiosis control, and (2) the rumen, for production indications. Absorption and distribution of monensin into the blood are therefore not clinically relevant to its efficacy. Monensin has no pharmacological effects in the animal other than those occurring in the digestive tract. Further, monensin is relatively insoluble in aqueous solutions.

CVM required Elanco to conduct large and complex studies in its supplemental applications for coccidiosis control and milk production efficiency in dairy cattle. Further, distinct studies were required for coccidiosis control, milk production efficiency in dairy cattle, and feed efficiency in beef cattle, supporting Elanco's contention that CVM has always required separate studies for these non-overlapping claims.

On July 1, 2019, CVM approved an ANADA (ANADA 200-639) filed by Huvepharma for Monovet 90, a generic monensin Type A medicated article that relied on Elanco's Rumensin as the Reference Listed New Animal Drug ("RLNAD"). The Freedom of Information ("FOI") Summary, ANADA 200-639, released by CVM on July 1, 2019, states that the Huvepharma

Monovet product was "determined to be bioequivalent to the RLNAD (Rumensin 90) using an approach that included:"

- A "comparison of product similarity [that] included an assessment of the qualitative (Q1), quantitative (Q2) and physicochemical (Q3) attributes" of Monovet;
- A single "*in vivo* clinical end-point bioequivalence study in cattle for the indication of feed efficiency;" and
- An "*in vitro* comparative dissolution across a range of conditions consistent with those encountered in the target species gastrointestinal tract."[2]

The single *in vivo* clinical end-point bioequivalence study was conducted "to demonstrate equivalence between the generic and RLNAD products for feed efficiency in crossbred beef steers."[3]

The treatment groups reported in the FOI Summary ANADA 200-639 are:[4]

A summary of treatment groups for study number H1701BB

Total # of Animals	# of Pens	Animals per Pen	Type of feed	Duration
200	20	10	Type C feed containing negative control article (placebo)	112 days
198	20	9 or 10*	Type C medicated feed containing positive control article (RLNAD)	
200	20	10	Type C medicated feed containing test article (generic)	

*Two animals, each from a different pen, were excluded on day zero and were not replaced due to unavailability of suitable replacement animals.

[2] CVM, Corrected Freedom of Information (FOI) Summary, ANADA 200-639 ("ANADA 200-639 FOI Summary"), at 6-7.

[3] *Id.* at 8.

[4] *Id.* at 9.

The reported study results[5] are:

Summary of the bioequivalence evaluation for feed efficiency (feed to gain ratio)

Treatment group	Least Square Means	Standard Error of the Mean
Un-medicated feed†	9.3496	0.09078
RLNAD	8.4824*	0.09112
Test Article	8.4005*	0.09058

†Negative control (placebo)
*Significantly different ($p<0.05$) in comparison to the negative article

The ratio of the means of Monovet® 90 to the RLNAD was 0.99 and the 90% confidence interval was [0.97, 1.02] which was contained within [0.80, 1.25].[6]

Huvepharma also conducted an *in vitro* dissolution study, "comparative dissolution of Monovet 90 and Rumensin type A medicated articles." According to the ANADA 200-639 FOI Summary, the study was conducted because "dissolution is considered the critical attribute which impacts the availability of monensin at the site of action."[7]

Key parameters of the study identified in the ANADA 200-639 FOI Summary are: pH of the media; unidentified USP buffers; use of Tween 80; slow rotation speed in dissolution vessels; and use of 45 mg of Type A monensin in dissolution vessels. As discussed further below, USP Tween 80 is not a bio-relevant medium, and the level of monensin used for the study is likely too low to be relevant to actual concentration in rumen.

The ANADA 200-639 FOI Summary reports the results of the *in vitro* dissolution study as follows:

> Stage 1 Results: In all cases the normalized data resulted in f_2' sameness criteria of ≥ 50. For the test conditions that did not attain 85% dissolution, the dissolution data (percent release of monensin) was normalized with the maximum dissolution attained assigned a value of 100% and the remaining data adjusted proportionately.

[5] *Id.* at 10.

[6] *Id*.

[7] *Id.* at 6.

Results of f_2' used for comparison of dissolution

Test condition	f_2'
	QA
TC1	80.85
TC2	56.42
TC3	70.10

QA = monensin A

> Stage 2 Results: All data across the three *in vitro* methods of product assessment successfully met the criteria for profile comparability based upon the TL approach.
>
> Dissolution profiles of 60 samples from five lots of Rumensin 90 were analyzed to establish the tolerance limits that sufficiently define the variability of dissolution in the approved RLNAD. The dissolution profiles of 36 samples from 3 lots of Monovet all fell within the tolerance limits established from the RLNAD data. The *in vitro* dissolution characteristics of the generic and RLNAD products met the criteria for equivalence of formulations and were determined to be comparable with respect to their respective rates and extent of API release across a range of *in vitro* conditions.[8]

CVM relied on the *in vitro* dissolution results to extrapolate the findings from the *in vivo* clinical end-point bioequivalence study across indications and dose levels. Toward this end, CVM states in the ANADA 200-639 FOI Summary:

> The cumulative data supports the bioequivalence between Monovet 90 and the RLNAD. Both formulations contain the same active ingredient in the same concentration and dosage form . . . Both formulations release monensin at the same rate and extent across a range of *in vitro* (dissolution) conditions, and both formulations have been shown to be bioequivalent under *in vivo* (clinical end-point bioequivalence study) conditions using an approved indication for the RLNAD in cattle. The proposed product is considered bioequivalent to the RLNAD.[9]

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[8] *Id.* at 13-14.

[9] *Id.* at 8.

B. Legal Framework

1. Absent An Adequate Showing of Bioequivalence, FDA Cannot Approve a Generic Animal Drug

Animal drug approval in the United States is, in many ways, analogous to human drug approval. The FDCA states, in relevant part, that a new animal drug will be presumed to be unsafe, and thus adulterated, unless it is has been approved by FDA.[10] A sponsor can obtain FDA's approval for an innovative animal drug by submitting a new animal drug application ("NADA") pursuant to section 512(b)(1) of the FDCA. Such applications must demonstrate that the new animal drug is safe and effective under its proposed conditions of use. Safety must be established through "adequate tests by all methods reasonably applicable" to the drug.[11] Effectiveness must be demonstrated by "substantial evidence,"[12] which is defined to mean "one or more adequate and well controlled investigations."[13] Performing all studies and compiling all data necessary to support an NADA takes many years and requires substantial investment by the sponsor.

Generic animal drugs do not undergo the same type of testing because FDA does not directly evaluate them for safety and effectiveness. Instead, as established by the 1988 Generic Animal Drug and Patent Term Restoration Act ("GADPTRA"), the sponsor of a generic animal drug may file an abbreviated new animal drug application ("ANADA") pursuant to section 512(b)(2) of the FDCA. The goal of an ANADA is to show that the generic drug will be "the same as" a previously approved animal drug, which is known as the reference-listed new animal drug ("RLNAD"). Based on this showing of sameness, FDA relies on its prior determination that the RLNAD is safe and effective to conclude that the generic animal drug also will be safe and effective under the same conditions of use.

To be approvable under this standard, an ANADA generally must show that, with certain exceptions, the generic animal drug:

(1) has the same active ingredient(s) as the RLNAD;

(2) has the same route of administration, dosage form, strength, and use with other animal drugs as the RLNAD;

(3) is bioequivalent to the RLNAD; and

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[10] FDCA § 512(a)(1).

[11] *Id.* § 512(d)(1)(A).

[12] *Id.* § 512(d)(1)(E).

[13] *Id.* § 512(d)(3).

(4) is proposed to have the same labeling as the RLNAD.[14]

Demonstrating bioequivalence is the most important aspect of an ANADA and the linchpin of FDA's approval of a generic animal drug. As defined by the FDCA, "bioequivalence" means "the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a new animal drug and becomes available at the site of drug action."[15] For a generic drug to be considered bioequivalent to the RLNAD, the ANADA generally must show that there are no "significant difference[s]" between the two drugs in the rate and extent of absorption.[16] Absent such a showing, FDA cannot reasonably conclude that a generic animal drug will have the same effect and safety profile as the RLNAD and, therefore, cannot approve the generic animal drug.

The FDCA provides additional, specific instructions for situations where FDA has determined that the rate of and extent of absorption cannot be directly measured. Where FDA determines that such measurement would be "inappropriate or impractical," the statute provides that bioequivalence can be shown by:

> an appropriate acute pharmacological effects test or other test of the [proposed generic animal drug], and when deemed scientifically necessary, of the [RLNAD] in the species to be tested or in an appropriate animal model . . . [17]

Bioequivalence may be shown if such an alternative test "does not show a significant difference between the [proposed generic drug] and [the RLNAD] when administered at the same dose under similar experimental conditions."[18]

A showing of bioequivalence is not optional. An ANADA approval in the absence of an adequate showing of bioequivalence is not in accordance with law and must be set aside.[19] Further, the proper vehicle to challenge an improvidently granted approval is a citizen petition. As the U.S. District Court for the District of Columbia has explained, "Congress has . . . furnished a . . . remedy appropriate for . . . plaintiffs claiming to be injured by or threatened with unwelcome competition in the marketplace on account of . . . [an inappropriate] decision to

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[14] *Id.* §§ 512(n)(1), 512(c)(2)(A).

[15] *Id.* § 512(c)(2)(H)(i).

[16] *Id.* § 512(c)(2)(H)(ii).

[17] *Id.* § 512(c)(2)(H)(ii)(III).

[18] *Id.*

[19] *See* 5 U.S.C. § 706(2)(A); *see also, e.g.*, *Cook v. FDA*, 733 F.3d 1, 10-11 (D.C. Cir. 2013) ("it follows apodictically" that FDA actions that violate the FDCA are "not in accordance with law" under the APA).

approve a competitor's application. That remedy is by [citizen petition] and possible judicial review."[20]

2. If Evidence Becomes Available to Show that a Generic Animal Drug is Not Bioequivalent to the RLNAD, FDA Must Initiate Steps for Withdrawal

Importantly, under the FDCA, the approval status of an ANADA is not immutable. Even if a generic animal drug was appropriately approved, the statute states clearly that an approval of an application for an animal drug must be withdrawn if, *inter alia*, new information reveals that the drug is not safe, or that there is a lack of substantial evidence of efficacy:

> The Secretary shall, after due notice and opportunity for hearing to the applicant, *issue an order withdrawing approval of an application filed pursuant to subsection (b)* with respect to any new animal drug if the Secretary finds—
>
> . . .
>
> (B) that new evidence not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved or that subparagraph (I) of paragraph (1) of subsection (d) applies to such drug; [or]
>
> (C) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that such drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.[21]

In the human drug arena, FDA's Center for Drug Evaluation and Research ("CDER") has initiated actions to withdraw generic drug approvals based on new information showing that the generic drug is not bioequivalent to the innovator product. Thus, for example, FDA proposed

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[20] *Hoffman-La Roche, Inc. v. Harris*, 484 F. Supp. 58, 65 (D.D.C 1979).

[21] FDCA § 512(e)(1)(B)-(C)(emphasis added); *see also* 21 C.F.R. § 514.115(b)(3); *cf. Cutler v. Hayes*, 818 F.2d 879, 893 n.116 (D.C. Cir. 1987) (noting that the equivalent withdrawal authority in the human drug context is "an enforceable statutory directive"); *Natural Resources Defense Council, Inc. v. FDA*, 760 F.3d 151, 158 (2d Cir. 2014) ("The text of [FDCA § [512(e)(1)] clearly requires withdrawal of approval once such a finding has been made.").

withdrawing approval of Mallinckrodt Inc.'s generic methylphenidate hydrochloride extended-release tablets on grounds that a post-approval bioequivalence study of the product suggested that bioequivalence was lacking.[22]

FDA has similarly requested that several generic manufacturers withdraw their generic buproprion hydrochloride products based on new studies demonstrating that the products were not bioequivalent to the reference listed drug ("RLD").[23] Similarly, FDA withdrew the approval for an Impax generic ursodiol product in 2019 after studies conducted by a contract research organization ("CRO") failed to demonstrate that the company's generic product was bioequivalent to the RLD, and after Impax did not respond to a request to submit new bioequivalence data.[24]

As discussed further below, new data call into question the bioequivalence of Monovet to Rumensin. FDA must therefore initiate proceedings under section 512(e)(1) of the FDCA and the agency's implementing regulations at 21 C.F.R. § 514.115(b) to withdraw approval Huvepharma's Monovet product.

3. FDA Must Adhere to its Published Bioequivalence Guidance Documents

FDA has not issued regulations delineating the specific procedures for assessing bioequivalence of animal drugs under section 512(n) of the FDCA. Instead, in guidance documents, CVM has referenced the bioequivalence regulations promulgated in 21 C.F.R. Part 320 for human drugs.[25] CVM also has issued detailed guidance establishing the requirements for demonstrating bioequivalence in generic animal drugs.[26]

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[22] 81 Fed. Reg. 71737 (Oct. 18, 2016); *see also* 81 Fed. Reg. 71741 (Oct. 18, 2016) (proposing to withdraw Kremers Urban Pharmaceuticals Inc.'s generic methylphenidate extended-release tablets on similar grounds).

[23] *See, e.g.,* 79 Fed. Reg. 19626 (April 9, 2014) (providing notice that Watson Laboratories, Inc. agreed to withdraw its generic buproprion hydrochloride pursuant to FDCA § 505(e)); 78 Fed. Reg. 16685 (Mar. 18, 2013) (providing notice that Impax Laboratories, Inc. ("Impax") agreed to withdraw its generic buproprion hydrochloride pursuant to FDCA § 505(e)).

[24] 84 Fed. Reg. 48625 (Sept. 16, 2019); *see also* 82 Fed. Reg. 38911 (Aug. 16, 2017) (indicating that FDA withdrew approval for Upsher-Smith Laboratories' (Upsher-Smith) generic zaleplon product because the company did not respond to the Agency's request for new bioequivalence studies after bioequivalence studies conducted by a CRO were called into question); 82 Fed. Reg. 41273 (Aug. 30, 2017) (indicating that FDA withdrew approval for Upsher-Smith's generic propranolol hydrochloride product on grounds that new studies conducted by a CRO showed that the generic was not bioequivalent to the RLD).

[25] *See, e.g.*, *FDA, CVM, Draft Guidance for Industry ("GFI") #171, Demonstrating Bioequivalence for Soluble Powder Oral Dosage Form Products or Type A Medicated Articles Manufactured from Active Pharmaceutical Ingredients Considered to be Soluble in Aqueous Media* (Sept. 2019) ("GFI #171").

[26] GFI #35; GFI #171.

Among other things, these guidance documents set forth CVM's considerations for waiving the requirement for *in vivo* bioequivalence studies for animal drugs manufactured from active ingredients considered to be water soluble,[27] and for the design and analysis of *in vivo* bioequivalence studies for generic animal drugs.[28]

While CVM designates its guidance as non-binding, that label is not controlling.[29] For several reasons, FDA's ability to depart from its published guidance is constrained. Pursuant to section 701(h) of the FDCA and FDA's implementing "Good Guidance Practice" regulations (codified at 21 C.F.R. § 10.115), "FDA employees may depart from guidance documents only with appropriate justification and supervisory concurrence."[30] Moreover, changes to an existing policy that are more than minor, address complex scientific issues, or cover controversial topics must be made through the procedures for "Level 1" guidance.[31] That process "must be followed whenever regulatory expectations that are not readily apparent . . . are first communicated to a broad audience."[32]

Perhaps more importantly, bedrock principles of administrative law "require agencies to follow their own rules" even those "that limit otherwise discretionary actions."[33] When an agency fails to follow its own "rules, regulations or procedures," then "its action cannot stand and courts will strike it down."[34] Similarly, the Administrative Procedure Act ("APA") prohibits agencies from departing from "a prior policy *sub silentio*" or from "disregard[ing] rules that are still on the books."[35] Indeed, an irrational or unexplained "departure from a governing policy constitutes action that must be overturned as arbitrary, capricious, or an abuse of discretion.'"[36]

FDA has issued clear guidance setting forth the required approach for demonstrating the bioequivalence of highly insoluble animal feed drugs, such as monensin. When approving

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[27] GFI #171.

[28] GFI #35.

[29] *See, e.g.*, *Philip Morris USA Inc. v. FDA*, 202 F. Supp. 3d 31, 46 (D.D.C. 2016).

[30] 21 C.F.R. § 10.115(d)(3).

[31] *Id.* § 10.115(c).

[32] *Id.* § 10.115(e).

[33] *Steenholdt v. FAA*, 314 F.3d 633, 639 (D.C. Cir. 2003) (citing *United States ex rel. Accardi v. Shaughnessy*, 347 U.S. 260 (1954)).

[34] *United States v. Heffner*, 420 F.2d 809, 811 (4th Cir. 1969); cf. *Emami v. Nielsen*, 365 F. Supp. 3d 1009, 1021 (N.D. Cal. 2019) (plaintiffs "adequately allege[d] that the State Department has not followed its own guidance").

[35] *FCC v. Fox Television Stations, Inc.*, 556 U.S. 502 (2009).

[36] *Venetian Casino Resort, L.L.C. v. EEOC*, 530 F.3d 925, 935 (D.C. Cir. 2008) (quoting *INS v. Yang*, 519 U.S. 26, 32 (1996)).

ANADAs for generic monensin, FDA is obligated to adhere to this guidance, or to develop and issue new guidance.

C. CVM Guidance and Precedent Make Clear that Two *In Vivo* Clinical End-Point Studies Are Required to Establish Bioequivalence of a Generic Monensin, Such as Monovet

1. FDA Has Set Forth Clear Requirements for Establishing Bioequivalence of an Insoluble Generic Animal Drug Such as Monensin

FDA guidance states that different approaches to bioequivalence (as defined in FDCA § 512(c)(2)(H)(i)) are appropriate depending on "the purpose of the study, the analytical method available, and the nature of the product."[37] In particular, "if drug concentrations in blood (or fluids or tissues) are not measurable or are inappropriate, and there are no appropriate pharmacologic effects that can be monitored, then a clinical end-point study may be conducted, comparing the test (generic) product to the reference (pioneer) product and a placebo (or negative) control."[38]

GFI #35 makes clear that design of a clinical end-point study should be based in the first instance on the identified target animal and the labeling claims of the RLNAD, including a consideration of whether the claims are overlapping in terms of dose:

> Studies should generally be conducted using the target animal species, with consideration for the sex, class, body weight, age, health status, and feeding and husbandry conditions, as described on the pioneer product labeling. In general, the length of time that the study is conducted should be consistent with the duration of use on the pioneer product labeling.
>
> In general, the response(s) to be measured in a clinical end-point study should be based upon the labeling claims of the pioneer product and selected in consultation with CVM. It may not be necessary to collect data on some overlapping claims (e.g., for a production drug which is added at the same amount per ton of feed for both growth rate and feed efficiency, data from only one of the two responses need be collected).[39]

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[37] GFI #35 at 8.

[38] *Id.*

[39] *Id.* at 23.

In other guidance, CVM affirms that beef cattle and dairy cattle are considered distinct food producing animals.[40] Notably, an application for the use of a previously-approved animal drug in a new target animal must be submitted as a Category II supplemental NADA and may require additional safety and efficacy data.[41] In this context, CVM's approval of Rumensin for lactating dairy cows specifically states that the approval is for a "new class of animals (dairy cows)."[42]

GFI #35 and prior case law make clear that dose selection should be the highest approved dose in the target animal species:

> [F]or products labeled for multiple claims involving different pharmacologic actions at a broad dose range (e.g., therapeutic and production claims), a single bioequivalence study *at the highest approved dose* will usually be adequate.[43]

GFI #35 states that *in vitro* dissolution studies have utility for the limited purpose of supporting approval for multiple strengths or concentrations of solid oral dosage forms:

> The generic sponsor should discuss with CVM the appropriate *in vivo* bioequivalence testing and *in vitro* dissolution testing to obtain approval for multiple strengths (or concentrations) of solid oral dosage forms.
>
> CVM will consider the ratio of active to inactive ingredients and the *in vitro* dissolution profiles of the different strengths, the water solubility of the drug, and the range of strengths for which approval is sought.
>
> One *in vivo* bioequivalence study with highest strength product may suffice if the multiple strength products have the same ratio of active to inactive ingredients and are otherwise identical in formulation.

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[40] *See FDA, Guidance for Industry, CVM GFI #191, Changes to Approved NADAs — New NADAs vs. Category II Supplemental NADAs*, at App'x III (Feb. 2020) ("GFI #191").

[41] *Id.* at 10.

[42] *See* CVM, FOI Summary, NADA 095-735 (Oct. 28, 2004).

[43] GFI #35 at 9 (emphasis added); *see also Alpharma, Inc. v. Leavitt*, 460 F.3d 1, 73 (D.C. Cir. 2006) (deferring to FDA's position in the October 27, 1995 letter from Ronald Chesemore, Associate Commissioner for Regulatory Affairs, to counsel for Alpharma, which stated that "FDA has recommended that, as a general rule, a bioequivalence study be conducted using the highest approved dose. This recommendation is based on the fact that formulation differences between an innovator product and a generic copy can be better evaluated at a high dose than at a low dose because at a high dose, the degree of assay specificity and sensitivity will have less impact on the assay results.").

> *In vitro* dissolution testing should be conducted, using an FDA approved method, to compare each strength of the generic product to the corresponding strength of the reference product.[44]

Type A medicated articles are not solid oral dosage forms and are not the final formulation presented to the animal (which is a Type C medicated feed). Therefore, dissolution testing should not be used to evaluate different concentrations of Type A medicated articles or to replace bioequivalence studies in different classes of animals.

Elanco has reviewed CVM's released FOI Summaries for generic Type A medicated article approvals over the past four years and has found no instance, other than the Monovet approval, in which *in vitro* dissolution studies were relied on to demonstrate bioequivalence. Further, CVM has previously been clear that while *in vitro* dissolution studies are appropriate for a formulation change of an approved Type A medicated article, such studies are not appropriate to bridge to a separate NADA or a new indication.

2. Bioequivalence of Generic Monensin Must Be Established By *In Vivo* Clinical End-Point Studies in Both Dairy Cattle and Beef Cattle, at the Highest Appropriate Labeled Dose

Consistent with GFI #35, CVM has previously taken the position that it is unlikely that a generic drug sponsor can demonstrate that monensin or monensin sodium is "soluble" using either the USP definition or a "dosage adjusted" approach, as described in CVM guidance on waivers for *in vivo* bioequivalence requirements for certain animal drugs and type A medicated articles.[45] In accordance with GFI #35, *in vivo* clinical end-point studies are therefore required to show the bioequivalence of a generic monensin product.

i. <u>A Clinical End-Point Study Must Be Conducted In Lactating Dairy Cattle Consistent with the Recommendation In GFI #35 That A Clinical End-Point Study Is Conducted At The Highest Dose Level</u>

Consistent with the directive in GFI #35 that a bioequivalence study should be conducted at the highest dose approved for the RLNAD, a clinical end-point study to demonstrate monensin bioequivalence should be conducted at the highest dosage level in cattle, which for Rumensin is 660 mg/hd/day (1.1 mg/kg bw/day) in the lactating dairy cow.

Rumensin is approved for increased milk production efficiency in dairy cows, to be fed in a total mixed ration containing 11 to 22 g/ton monensin, or in Type C Medicated Feed containing 11 to 400 g/ton monensin to provide 185 to 660 mg/hd/day monensin to lactating cows.

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[44] GFI #35 at 9.

[45] *See* Letter from CVM to Elanco (July 18, 2007) (citing a prior version of current FDA draft guidance) [Tab 1]; GFI #171 (current draft guidance).

Rumensin is approved for cattle fed in confinement for slaughter, to be fed in a complete feed that contains 5 to 40 g/ton monensin to provide 50 to 480 mg/hd/day monensin.

Other Rumensin approvals including for calves, growing cattle, mature reproducing beef cows, and for coccidiosis control have an upper limit of 200 mg/hd/day of monensin.

The highest dose in beef cattle based on an average industry live slaughter weight of 550 kg would be 0.87 mg/kg bw/day of monensin compared to 1.1 mg/kg bw/day in the average lactating dairy cow of 600 kg.

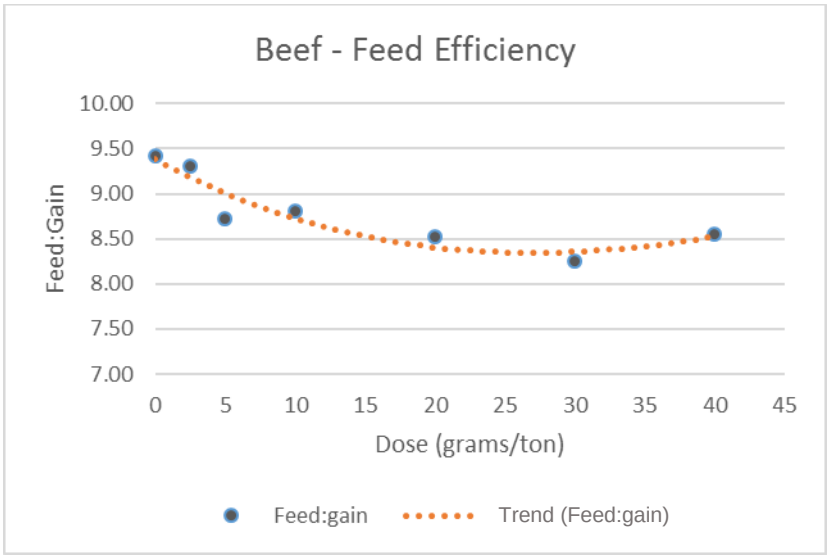
Cattle	Highest Dose (mg/hd/day)	Mature Body Weight (kg)	Dose at Mature Body Weight (mg/kg bw /day)
Dairy	660	600	1.1
Beef	480	550	0.87

Clinical end-point studies should be conducted at a dose selected in the linear part of the dose response curve. If a dose is selected that falls on a flat part of the dose response curve, it will not be possible to distinguish if the test product (generic) is equivalent to the reference product (RLNAD) as any changes in the dose would have no effect on efficacy (such as seen in beef cattle between 20 and 40 g/ton).[46]

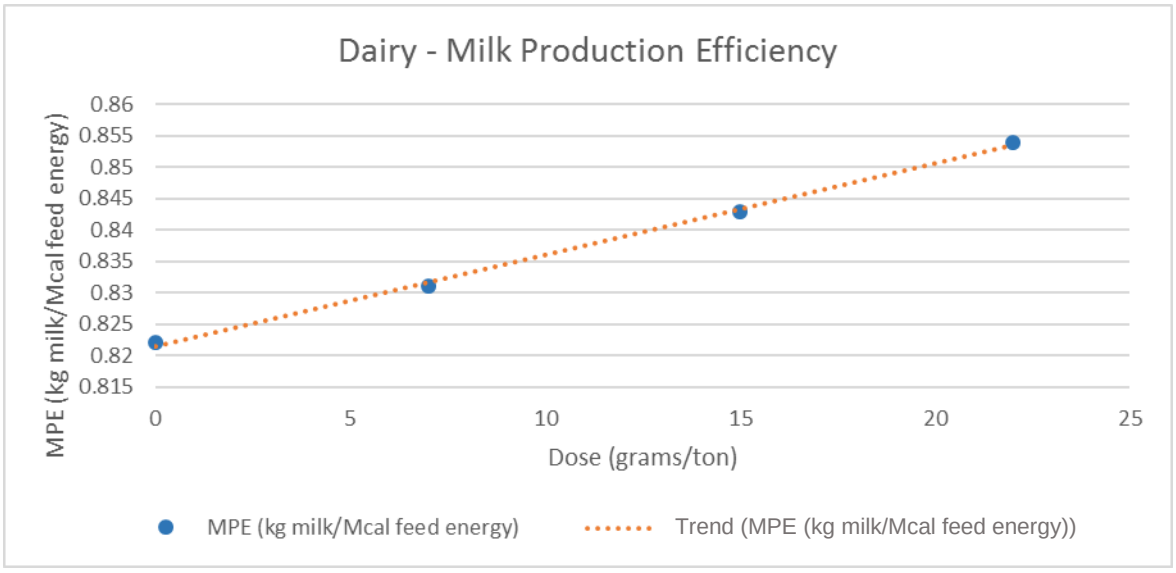
The Rumensin dose response curve for feed efficiency in beef cattle shows a flat portion from in the range of 20 to 40 g/ton. Studies conducted to support the Rumensin NADAs showed no difference in feed efficiency of cattle fed monensin at 20 g/ton compared to those fed at 30 g/ton or 40 g/ton.[47] However, feeding 40 g/ton monensin did improve feed efficiency when compared to controls. These results demonstrated that 40 g/ton monensin did not depress animal response below that of the previously determined most effective dose. Thus, the 20 g/ton to 40 g/ton dose of monensin for feed efficiency in beef cattle is in the flat portion of the dose response curve.

[46] E. Bermingham et al., "Demonstrating bioequivalence using clinical studies," 35 J. Veterinary Pharmacology and Therapeutics, supp. 1, at 31 (2012) [Tab 2].

[47] CVM, FOI Summary, NADA 095-735 (Oct. 28, 2004).



The Rumensin dose response curve for milk production efficiency (MPE) in lactating dairy cows shows a linear response across all dose levels. The chart below shows MPE expressed as kg of milk produced per energy intake from the feed, which was the calculation used in the Rumensin NADA approval for dairy cattle. The linear, upward trend line indicates improved MPE as dose increases.



It has been established that *in vivo* bioequivalence studies should be conducted at the highest dose in the target species, which is in lactating dairy cows in the case of Rumensin. These dose response curves support that a bioequivalence study should be done at the highest dose in lactating dairy cows, which is on the linear part of the dose response curve.

The *in vivo* clinical end-point bioequivalence study for Monovet evaluated the feed efficiency response in beef cattle monensin at 30 g/ton. The study fails to provide substantial evidence of efficacy as it was conducted in beef cattle instead of dairy cattle, and at a dose that was on the flat part of the dose response curve for beef cattle.

ii. <u>As Previously Acknowledged by CVM, Coccidiosis Control and Feed Efficiency are Not Overlapping Claims and Therefore Two Clinical End-Point Studies Are Appropriate for Generic Monensin</u>

In direct correspondence with Elanco, CVM has taken the position that two clinical end-point studies will be required to establish the bioequivalence of a generic monensin product. In particular, CVM has explained:

> CVM has determined that two clinical-end point studies would be required to adequately assess [monensin] product bioequivalence: 1) one for weight gain or feed efficiency in beef cattle, or milk production efficiency in dairy cattle; and 2) one for prevention and control of coccidiosis in beef cattle.
>
> An evaluation of physiological differences between classes of animals is an essential assessment in the regulatory review of innovative new drugs. But when evaluating bioequivalence between products that are administered orally, our concern is to assess the formulation effects and whether or not there is the potential for a formulation-by-breed/class interaction. In the absence of reasons to suspect that such interactions will occur, we have no reason to recommend additional studies. In the case of monensin Type A medicated article, the simplicity of the formulation renders it highly unlikely that a food-by-formulation effect will be present in ruminating cattle. *Therefore, we have determined that an evaluation of one production claim and one therapeutic claim in cattle is sufficient to assess product bioequivalence to RUMENSIN Type A medicated article.*[48]

CVM's stated position is consistent with the fact that a monensin claim for the control of coccidiosis does not overlap with the other claims. Monensin is not a production drug when used for prevention and control of coccidiosis. Control of coccidiosis depends on the interaction of the drug with sporozoites of *Emeria* species in the lumen of the small intestine, while effects

[48] Letter from CVM to Elanco (Jan. 6, 2010) (emphasis added) [Tab 3].

on growth and feed efficiency depend on interactions with the microbial population in the rumen. Coccidiosis primarily affects young animals prior to the development of immunity (with occasional breaks in older animals when the immune system is compromised). This is in contrast to the production claims which apply to cattle across a broad range of ages.

Energy and nutrient metabolism are profoundly different between lactating dairy cattle, dry cows, and growing beef animals. This is illustrated by experiments in which cattle underwent blood vessel catheterization along the digestive tract and liver to measure nutrient uptake and output. For example, Eisemann and colleagues measured nutrient fluxes in beef steers at three stages of growth,[49] while Reynolds and colleagues compared late gestation and lactation in dairy cattle.[50] Table l shows minimum and maximum values for steers during growth from 236 to 522 kg body weight and comparable data for dairy cows in the late dry period and near peak lactation. Dry matter intake by growing steers near their mature weight was similar to dry cows, while cows near peak lactation consumed almost twice as much on a dry matter basis. Generally, blood flows and nutrient fluxes across the portal-drained viscera and liver in dry cows in late gestation were similar to the maximum values found in growing beef animals. Blood flows and uptake of volatile fatty acids from the digestive tract into portal blood was higher in lactating dairy cows than either dry cows or growing beef cattle. There was no net uptake of glucose from the digestive tract, so the glucose required for lactose synthesis came entirely from gluconeogenesis. This is reflected in a markedly higher uptake of propionate, and output of glucose, by the liver in lactating cows.

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[49] J.H. Eisemann et al., “Patterns of nutrient exchange and oxygen use among portal drained viscera, liver and hindquarters of beef steers from 235 to 525 kg body weight,” 74 J. Anim. Sci. 1812 (1996) [Tab 4].

[50] C.K. Reynolds et al., “Splanchnic metabolism of dairy cows during the transition period from late gestation through early lactation,” 86 J. Dairy Sci. 1201 (2003) [Tab 5].

Table 1. Splanchnic Metabolism In Growing Beef Steers and Dairy Cows in Late Gestation and Lactation[51]

		Beef Steers	Dairy Cows	
		236 to 522 kg average body weight	Day Relative to Calving	
			-19	83
Dry Matter Intake (kg/d)		5.8 to 9.9	9.6	22.I
Production (kg/d)	Milk	-	-	40.7
	Milk Fat	-	-	1.543
	Milk Protein	-	-	1.282
	Milk Lactose	-	-	1.917
Blood Flow (L/h)	Portal Vein	560 to 884	964	2093
	Liver	683 to 981	1121	2437
Net Flux of Metabolites Across the Portal Drained Viscera (mmol/h)	Glucose	-2 to -66	-24.6	-4.7
	BHBA	90 tol 71	127	299
	Acetate	776 to 1294	1446	3374
	Propionate	275 to 413	343	1220
	Butyrate	68 to 106	46	223
Net Flux of Metabolites Across the Liver (mmol/h)	Glucose	159 to 273	294	840
	BI-IBA	54to 176	151	275
	Acetate	247 to 624	313	490
	Propionate	-229 to -383	-322	-1156
	Butyrate	-53 to -86	-37.7	-185.1

The dairy cows in the experiment of Reynolds and colleagues produced more than 1.5 kg of fat, 1.2 kg protein and 1.9 kg of carbohydrate (lactose) via the milk of over a 24 hour milking cycle (Table 1). This is typical of production for lactating Holsteins near the peak of lactation. In contrast, a 300 kg steer with a shrunk weight gain of 1.3 kg/day deposits approximately 140 g of protein and 460 g of fat and negligible carbohydrates in daily carcass gain. This translates to the lactating dairy cow producing more than three times as much fat and at least eight times as much protein as the growing animal beef animal deposits in carcass gain each day. The high level of milk production and the high nutrient intakes needed by lactating dairy cows to sustain this level of production demand very different ration formulation and feeding strategies from beef animals. Notably, the National Research Council ("NRC") finds it necessary to issue separate recommendations on the nutrient requirements of each class of animal.[52]

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[51] Eisemann, *supra* note 49 [Tab 4]; Reynolds, *supra* note 50 [Tab 5].

[52] *See* NRC, NUTRIENT REQUIREMENTS OF BEEF CATTLE (7th rev. ed., Update 2000) (2000) [Tab 6]; NRC, NUTRIENT REQUIREMENTS OF DAIRY CATTLE (7th rev. ed.) (2001) [Tab 7].

Lactation renders the cow more susceptible to a wider range of health hazards than growing beef animals. Mastitis is an obvious example, but the stress of transition to from the dry to lactating state, and mobilization of body tissues to support milk production in early lactation, are also accompanied by an increased risk of milk fever, displaced abomasum, fatty liver and ketosis. Immune function is impaired, increasing the risk of infectious disease. The cow must also conceive the next calf while under great production stress.

There are many different factors that lead to modifications in the pharmacokinetics and/or pharmacodynamics of a pharmaceutical compound. As a result, these changes could lead to differences in the target animal safety or residue depletion profile. These differences are in cytochrome P-450 (CYP) isoform expression (monensin is suggested to be metabolized by the CYP3A subfamily), renal and hepatic physiology, p-glycoprotein expression, and gastrointestinal physiology to name just a few.[53] There are also many different class-related factors, such as regional blood flow, intrinsic hepatic metabolism, and renal clearance that lead to differences in the elimination of xenobiotics (therapeutics, nutrients, environmental toxins) and thus, possibly decrease the activity of a compound.[54] These physiological differences manifest themselves in significant differences in pharmacokinetic parameters between lactating and non-lactating cattle as reported for ceftazidime and ketoprofen.[55]

These differences make extrapolation of pharmacokinetic data very difficult from one species to another, with recent information indicating breed differences in cattle

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[53] J.D. Baggot & Q.A. McKellar, "The absorption, distribution and elimination of anthelmintic drugs: the role of pharmacokinetics," 17 J. Veterinary Pharmacology and Therapeutics 409 (1994) [Tab 8]; R.R. Dalvi et al., "Hepatic cytochrome P-450 dependent drug metabolizing activity in rats, rabbits and several food producing species," 10 J. Veterinary Pharmacology and Therapeutics 164 (1987) [Tab 9]; M. Giantin et al., "Effect of Breed upon Cytochromes P450 and Phase II Enzyme Expression in Cattle Liver," 36 Drug Metabolism and Disposition 885 (2008) [Tab 10]; D.R. Hennessy, "The disposition of antiparasitic drugs in relation to the development of resistance by parasites of livestock," 56 Acta Tropica 125 (1994) [Tab 11]; K.W. Hinchcliff et al., "Ruminant pharmacology," 7 Veterinary Clinics of N. Am.: Food Animal Practice 633 (1991) [Tab 12]; T.T. Kararli, "Comparison of the Gastrointestinal Anatomy, Physiology, and Biochemistry of Humans and Commonly Used Laboratory Animals," 16 Biopharmaceutics & Drug Disposition 351 (1995) [Tab 13]; C.E. Lanusse & R.K. Prichard, "Relationship between pharmacological properties and clinical efficacy of ruminant anthelmintics," 49 Veterinary Parasitology 123 (1993) [Tab 14]; C.R. Short, "Consideration of sheep as a minor species: comparison of drug metabolism and disposition with other domestic ruminants," 36 Veterinary and Human Toxicology 24 (1994) [Tab 15]; C.R. Short et al., "The oxidative metabolism of fenbendazole: a comparative study," 11 J. Veterinary Pharmacology and Therapeutics 50 (1988) [Tab 16].

[54] S. Modric et al., "Considerations for extrapolating *in vivo* bioequivalence data across species and routes, 35 J. Veterinary Pharmacology and Therapeutics, supp. 1, at 45 (2012) [Tab 17]; Short, *supra* note 53 [Tab 15].

[55] L. Igarza et al., "Some Pharmacokinetic Parameters of R-(-)- and S-(+)-Ketoprofen: The Influence of Age and Differing Physiological Status in Dairy Cattle," 28 Veterinary Research Communications 28 (2004) [Tab 18]; R. Rule et al., "The pharmacokinetics of ceftazidime in lactating and non-lactating cows," 20 Veterinary Research Communications 543 (1996) [Tab 19].

pharmacokinetics.[56] Extrapolation of pharmacokinetic data from one species to another is done commonly in the human drug discovery process where drug absorption data is extrapolated from rodents, dogs, and non-human primates to humans.[57] Published reports have shown that allometric predictions of clearance in large animal species were found to pose substantially greater risks of inaccuracies when compared with that observed for humans. Unlike in humans, for large animal species correction factors could not be applied because there was no trend between the exponents of simple allometry and the appropriate correction factor for improving the predictions.[58] Another point of consideration is the interspecies differences in the contribution of various organ systems and differences in body composition as it pertains to the body weight estimates. For example, when using ruminants in an allometric evaluation, it is important to consider the percentage of the estimated value of weight that is associated with rumen fluids. In a dairy cow the rumen capacity for feed and water can vary from 125 kg in a dry cow to 170 kg in a lactating cow.[59] From these values, it is clear that certain species-specific anatomical traits can greatly influence the accuracy of the predicted clearance. Modric and colleagues went on to state that inter- and intra- species differences are not only numerous, but more importantly, unpredictable, making safe and reliable comparisons of data for establishing bioequivalence a very difficult task to accomplish with the corollary applied to pharmacological response.[60]

Monensin is approved for dry and lactating dairy cows. This allows it to be fed continually throughout the production cycle. In its approval of Rumensin for lactating dairy cows, FDA required distinct efficacy studies for production and coccidiosis control. For production, Elanco demonstrated substantial evidence of efficacy through studies at nine trial sites, utilizing a total of 966 cows, for more than one lactation (13 – 18 months), in addition to human food safety studies quantifying monensin residue levels in tissue and milk and target animal safety studies.[61] For coccidiosis control, Elanco conducted additional effectiveness studies including a four site dose titration. Target animal safety and human food safety were not required as the feeding levels and rates were the same as the original approval.[62]

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[56] *See* Giantin, *supra* note 53 [Tab 10]; Modric, *supra* note 54 [Tab 17]; J. Sallovitz et al., "Breed differences on the plasma availability of moxidectin administered pour-on to calves," 164 Veterinary J. 47 (2002) [Tab 20]; L.H. Sumano et al., "Non-bioequivalence of various trademarks of enrofloxacin and Baytril® in cows," 108 Dtsch. Tierärztl. Wschr. 311 (2001) [Tab 21].

[57] S.L. Lindstedt et al., "Use of allometry in predicting anatomical and physiological parameters of mammals," 36 Laboratory Animals 1 (2002) [Tab 22].

[58] I. Mahmood et al., "Interspecies allometric scaling. Part I: prediction of clearance in large animals," 29 J. Veterinary Pharmacology and Therapeutics 415 (2006) [Tab 23].

[59] A.F. Park et al., "Characterization of ruminal dynamics in Holstein dairy cows during the periparturient period," 95 J. Animal Physiology and Animal Nutrition 571 (2011) [Tab 24].

[60] Modric, *supra* note 54 [Tab 17].

[61] *See* CVM, FOI Summary, NADA 095-735 (Oct. 28, 2004).

[62] *See* CVM, FOI Summary, NADA 095-735 (Oct. 22, 1990).

Based on differences in site of drug action, class, age, health status, feeding and husbandry conditions and duration of drug use, it is evident that multiple clinical end-point studies would be needed to demonstrate bioequivalence of alternative sources of monensin for control of coccidiosis and for the production claims in beef and dairy cattle.

For example, Parnell Veterinary Pharmaceuticals ("Parnell") received approval for a generic estrous synchronization product and were required to conduct *in vivo* studies in both beef and dairy cattle at multiple locations.[63] The application included an indication for use with cloprostenol sodium to synchronize estrous cycles to allow for fixed time artificial insemination ("FTAI") in lactating dairy cows and beef cows. This was a new indication, and to demonstrate substantial evidence of efficacy and safety, Parnell was required to conduct multi-center field studies in both mature reproducing beef cows and lactating dairy cows.

The rationale for conducting blood level or clinical end-point bioequivalence studies in both beef and dairy cattle is based on established and demonstrated physiological differences between these two classes of cattle. It is also important to note that there are distinct differences in nutritional requirements and animal management systems between beef and dairy cattle. Therefore, it is not scientifically justified that a demonstration of bioequivalence in beef cattle would suffice for extrapolating bioequivalence to dairy cows. For the approval of Monovet, Huvepharma conducted an *in vivo* clinical end-point bioequivalence study in feedlot steers, which was inappropriately utilized as evidence for demonstrating bioequivalence in lactating dairy cows.

D. The Huvepharma Monovet Approval Deviates Sharply From FDA Guidance and Precedent and Does Not Ensure that Monovet Has the Same Safety and Efficacy as the RLNAD, Rumensin

1. A Single Clinical End-Point Study in Beef Cattle is Insufficient

Despite CVM guidance, Huvepharma conducted only a single clinical end-point bioequivalence study evaluating production efficiency in beef cattle.[64] Huvepharma did not conduct a study in dairy cattle and did not conduct a study to evaluate the therapeutic end-point on coccidiosis control. This approach is a flagrant departure from CVM's explicit statement that production efficiency and coccidiosis are non-overlapping claims and thus must be studied in two separate clinical end-point studies. Huvepharma's approach is also inconsistent with long established CVM practice of treating dairy and beef cattle as distinct target animals for bioequivalence purposes.

As referred to in Section C above, Elanco was required to conduct efficacy and safety studies in dairy cows although beef approvals had been granted years earlier. This

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[63] *See* CVM, FOI Summary, ANADA 200-541 (Jan. 17, 2013).
[64] ANADA 200-639 FOI Summary, at 8.

demonstration of substantial evidence was needed due to the physiological differences between these two classes of cattle.

Further, the dose used by Huvepharma in its clinical end-point study in beef cattle is too high to allow for a definitive conclusion about bioequivalence. As discussed above, feed efficiency for beef cattle plateaus between a mid-range dose and a high dose. Thus, a clinical end-point study that relies on any dose between the mid and high to demonstrate production efficiency does not demonstrate bioequivalence – the target beef cattle may simply be receiving more monensin than necessary.

As demonstrated above in Section C.2.i, Rumensin data shows that feed efficiency does not improve when moving from a 20 g/ton dose to the highest level, a 40 g/ton dose. In contrast, as the dose increases in dairy cattle from the mid- to high dose, there is a clear production efficiency response. Therefore, a study utilizing the highest dose in dairy cattle would be sufficiently sensitive to show bioequivalence for production efficiency.

In addition, Huvepharma's clinical end-point study used a non-typical ration design, further undermining any conclusions that may be drawn about bioequivalence. In the Huvepharma study, the feed-to-gain ratio of the control beef cattle was 9.35; for the Rumensin treated beef cattle it was 8.48, and for the Monovet test article, 8.40. These feed-to-gain ratios were common in the 1970s, as demonstrated by the feed efficiency results in the original Rumensin NADA approval in Section C.2.i. Since the 1970s, changes in genetics and nutrition have improved the feed efficiency of beef cattle. Industry-wide data over the past 20 years indicates the average feed efficiency in feedlot cattle ranges from 6.0-6.5.[65]

The elevated feed-to-gain ratio in the Huvepharma study suggests that the beef cattle in the study were fed low energy rations. While both Rumensin- and Monovet-fed cattle significantly improved feed conversion compared to control, this study lacks relevance because it does not adequately represent typical cattle industry feeding practices. The ration fed to the cattle has a direct impact on ruminal fermentation, eating behaviors, and digestive issues. Monensin's mode of action is in the rumen, where it shifts the microbial population to provide more energy output. The rumen environment is much different in cattle fed a low energy ration, such as the one used in the Huvepharma study, compared to a typical high energy ration. Evaluating the equivalence in a low energy ration feeding scenario and on the flat part of the dose response curve does not necessarily demonstrate equivalence in a typical high energy ration feed practice.

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[65] *See* Beef Research Council of Canada, "Optimizing Feedlot Feed Efficiency" http://www.beefresearch.ca/research-topic.cfm/optimizing-feedlot-feed-efficiency-8 (showing a feed efficiency of 6.1) [Tab 25]; D. Shike, "Beef Cattle Feed Efficiency" (2013), available at https://lib.dr.iastate.edu/cgi/viewcontent.cgi?article=1027&context=driftlessconference [Tab 26]); Kansas State University Agricultural Experiment Station and Cooperative Extension Service, "Focus on Feedlots: Kansas Feedlot Performance and Feed Cost Summary, 2017 Annual Review" (Sept. 2018), available at https://bookstore.ksre.ksu.edu/pubs/MF3247.pdf [Tab 27].

Taking these factors into consideration, the single clinical-end point study examining only production efficiency at the highest dose in beef cattle being fed non typical rations is insufficient to draw conclusions about the bioequivalence of Monovet to Rumensin.

2. An *In Vitro* Dissolution Study is Insufficient to Extrapolate Bioequivalence Across Label Claims and Target Animals

CVM typically reviews *in vitro* dissolution studies when a NADA holder is testing different strengths or concentrations of a formulation or making a manufacturing change. There is no precedent for using *in vitro* dissolution studies as a replacement for bioequivalence studies. Moreover, the USP Tween 80 media, used by Huvepharma in its *in vitro* dissolution study, is a surfactant that increases solubility. Tween 80 is generally used when an applicant is making changes and seeks to establish that a new formulation or manufacturing change has not affected the product; it is not bio-relevant, however, and therefore should not be used in a dissolution study intended to establish bioequivalence.

In addition, the Monovet dissolution study utilized an alternative statistical method to establish similarity utilizing tolerance limits. This procedure is different than the standard f1 and f2 calculations described in FDA's guidance on dissolution testing for immediate release for solid dosage forms.[66] In that guidance, FDA describes a statistical method which necessitates that variation in dissolution results is acceptably low. The Monovet study did not use the standard statistical method and instead used a tolerance limit method due to the high within-lot variation (RSD>10). The tolerance limit method used in the Monovet study allows for a wider range to establish similarity.

Elanco conducted its own comparative dissolution study of Huvepharma's marketed Monovet product and Rumensin. The study was conducted in bio-relevant media to simulate both the rumen of beef cattle and dairy cattle. This study is summarized in **Appendix 1**. The results of the Elanco study suggest that the *in vitro* dissolution of Monovet is significantly different than that of Rumensin. The Elanco study used the current USP recommended bio-relevant media (USP 42-NF 47: Chapter 1236), typical to dairy cattle and beef cattle.

Ultimately, the difference in results between the Elanco *in vitro* dissolution study and the Huvepharma *in vitro* dissolution study undermine the utility of the Huvepharma study for establishing bioequivalence across labeling claims and target animals. Dissolution study results are greatly influenced by the selection of media and other conditions. This variation in dissolution methods makes it prone to scientific manipulation, and therefore should not be used to establish bioequivalence across labeling claims and target animals. The results also make clear that it is important to conduct studies in both beef cattle and dairy cattle because the distinct character of the rumen may affect the bioavailability of monensin.

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[66] *See FDA, Guidance for Industry, Dissolution Testing of Immediate Release Solid Oral Dosage Forms* (Aug. 1997).

3. The Net Result is That Clinical End-point and *In Vitro* Dissolution Studies Conducted by Huvepharma Provide No Assurance that Monovet is Bioequivalent to Rumensin

The single *in vivo* clinical end-point study in beef cattle is insufficient to demonstrate bioequivalence for monensin Type A medicated articles across labeling claims and target animals. The coccidiosis control and feed efficiency labeling claims are non-overlapping and, as acknowledged by CVM, require two clinical end-point studies: one for the therapeutic claim and one for the production efficiency claim.[67]

Moreover, a clinical end-point study should have been conducted in dairy cattle. Dairy cattle have a different dose response curve than beef cattle and the high dose is more sensitive than in beef cattle. The non-typical ration design is insufficiently sensitive to demonstrate comparative production efficiency.

Huvepharma's *in vitro* dissolution study is insufficient as the basis for extrapolating bioequivalence across labeling claims and target animals. It is unprecedented to use *in vitro* dissolution as the basis for determining bioequivalence of generic Type A medicated articles. An *in vitro* dissolution study conducted in bio-relevant media conducted by Elanco yielded very different results from the Huvepharma study. These distinct results call into question the use of the Huvepharma study as the basis of bioequivalence.

4. In Addition, as Tested by Elanco, Monovet is Not Comparable to Rumensin in Terms of Particle Size

The ANADA 200-639 FOI Summary reports that Monovet has "comparable physicochemical properties to the RLNAD, and that particle size distribution was evaluated over a 100 – 800 µm range."[68] However, testing conducted by Elanco shows there to be a significant difference in particle size between Monovet and Rumensin.

Data from tests conducted by Elanco of five Rumensin lots (P1-P5) and two Monovet lots (A1 and A2) are provided in the table below. Monovet lots include more fine particles (<125 µm) than Rumensin (16.9% and 3.3%, respectively) and fewer particles in the range of 180 - 850 µm than Rumensin (66.6% and 92.4%, respectively).

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[67] *See supra* Part II.C.2.ii.

[68] ANADA 200-639 FOI Summary, at 7.

	% Retained			
Lot ID	U.S. 20 Sieve (850 µm)	U.S. 80 Sieve (180 µm)	U.S. 120 Sieve (125 µm)	Pan (<125 µm)
Rumensin, P1	0.2	88.8	5.8	4.9
Rumensin, P2	0.1	92.3	4.7	2.7
Rumensin, P3	1.1	96.1	1.3	1.3
Rumensin, P4	0.0	91.9	4.3	3.7
Rumensin, P5	0.1	91.3	4.7	4.1
Average	0.3	92.1	4.2	3.3
Monovet, A1	0.1	72.4	13.3	14.4
Monovet, A2	0.0	60.7	20.1	19.3
Average	0.05	66.6	16.7	16.9

Particle Size analysis was performed using a Ro-Tap Sieve Shaker (Model RX29, W.S. Tyler Inc, Mentor OH, USA) equipped with 8-inch US Sieves 20 (850 µm), 80 (180 µm), 120 (125 µm) and the pan. Approximately 100 g of sample was entered into the top sieve of the stack of sieves, each with a finer screen and pan on the bottom. The stack of sieves was vibrated for 10 min. The amount of material in each sieve was measured to determine the percentage of sample that was retained on each sieve or filtered all the way to the pan at the bottom.

This data indicates a possible lack of consistency in the mixing of Type C Feeds from the Monovet Type A Medicated Article. This cannot be confirmed due to the lack of particle size distribution and Type C mixing data in ANADA 200-639 FOI Summary.

E. Conclusion

Taken together, these differences are significant and may affect users' experience with the generic Monovet product. Moreover, ultimately, there is no assurance that Monovet will have the same safety and efficacy as Rumensin.

Producers and animal health professionals look to FDA to ensure that products approved are safe and effective for their intended uses. The data used for the approval of

Huvepharma's Monovet is insufficient and provides no assurance that the product will perform in a manner that is the same as Rumensin.

Elanco respectfully asks that CVM commence withdrawal procedures for Huvepharma's ANADA for Monovet pursuant to FDCA § 512(e)(1). As described above, the information in the Huvepharma ANADA does not provide sufficient evidence that Monovet is bioequivalent to Rumensin. Further, new information from the comparative *in vitro* dissolution study conducted by Elanco, and described herein in Appendix I, undermines CVM's prior finding of bioequivalence, and requires that CVM take action.

In addition, consistent with 21 C.F.R. 10.115(d)(3) and the APA, Elanco asks that FDA refrain from approving future ANADAs for generic monensin Type A medicated articles unless and until either: (1) the ANADA includes at least two clinical end-point bioequivalence studies consistent with existing GFI #35; or (2) CVM issues a new guidance specifying an alternative approach to demonstrating bioequivalence.

III. ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to categorical exclusion under 21 C.F.R. § 25.33.

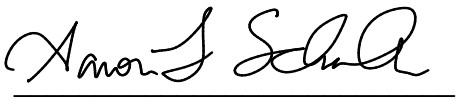
IV. ECONOMIC IMPACT

Pursuant to 21 C.F.R. § 10.30(b), an economic impact statement will be submitted upon request of the Commissioner.

V. CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully Submitted,



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May 28, 2020

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857

RE: Citizen Petition from Elanco Animal Health

Dear Sir or Madam:

Elanco Animal Health ("Elanco") submits the enclosed Citizen Petition and accompanying exhibits, to the U.S. Food and Drug Administration ("FDA") to request that the Agency take important steps with regard to its approval of generic versions of Elanco's Rumensin® (monensin) Type A medicated article.

Please direct all correspondence relating to this petition to me at the address provided above. Thank you for your consideration of this citizen petition.

Sincerely,

Aaron L. Schacht
Executive Vice President – Innovation, Regulatory & Business Development
Elanco Animal Health