Clinical pharmacology - navigation tools for a world filled with generic options

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Abstract

Understanding the basic types of drug product approval applications can be helpful when selecting products to recommend for use within a particular livestock system. Products that do not have an NADA or ANADA number have not been through any type of FDA approval process. Products with an ANADA, commonly referred to as "generics", have an abbreviated approval process through the FDA. Many products necessary for daily practice are listed in the FDA's *Green Book*. This document gives several examples of specific approval types, and how that relates to the effectiveness evidence for the product in the bottle. Both a solid understanding of the effectiveness evidence generated by the approval process, as well as the context within which the product will be used is necessary to make recommendations for use of these products within livestock systems.

Key words: clinical pharmacology, generic drug approvals

Types of FDA approval

There are 2 main types of FDA approval processes relevant to understanding the product options on the market today. The first is a novel product approval. When evidence for these new products is submitted to the FDA, they are given a NADA (new animal drug application) number. This unique number specifically identifies the product throughout the approval and marketing process. When a product reaches the end of its exclusive marketing time period, other companies can then legally market "generic" products. These applications are given an ANADA (abbreviated new animal drug application) number. These products must be manufactured in FDA-approved facilities, of which there were 1,788 facilities in the world in 2018.[1] There are a set of standards for FDA approved manufacturing facilities that will not be discussed here, but are extensive. A graphical representation of approved products is shown in Figure 1.

NADA process

There are 7 sections submitted as part of a NADA application:[3]

- Chemistry manufacturing and controls
- Effectiveness
- Target animal safety
- Human food safety
- Environmental Impact
- Labeling
- Other information

The information provided in these sections is extensive and details the manufacturing process with all of the quality controls.[3] It also describes the evidence available for the effectiveness of the product, summarizes the studies done to indicate the safety of the product even when given at 3× or 5× the label dose, establishes withdrawal times necessary to ensure human food safety, and describes any relevant environmental impacts of the drug. Additionally, it details the product label with all of the precautionary statements. Finally, it includes a section where any other information relevant to the drug can be submitted.

ANADA process

In order for a product to qualify for an abbreviated approval the active ingredient, concentration, dosage form, and route of administration have to be identical to an already approved product.[3] The evidence submitted for an abbreviated approval is very similar to that of the original pioneer product. However, the studies for each section do not need to be repeated if they are still applicable to the new product. For example, if the product formulation is identical to the original, the studies to establish meat and milk withdrawal times do not need to be repeated. The abbreviated application will simply reference the original pioneer product application.

The main difference between an ANADA and NADA approval processes is for the category of efficacy. The pioneer product must demonstrate direct evidence of efficacy, while a product approved by an ANADA must demonstrate bioequivalence. There are 2 common methods for demonstrating bioequivalence:[2] the first, and most common, is by a "biowaiver". This means that the FDA decided that the ingredients (both active and inactive) are so similar to the original that no further evidence other than the documentation of the chemical and manufacturing process. The studies from the original approval are cited as efficacy for the new product. If the product is not eligible for a biowaiver, then bioequivalence must be demonstrated by an additional method. There are multiple ways of doing this depending on product type. One of the most common methods is to establish bioequivalence by means of demonstrating that the new product has "equivalent" pharmacokinetic parameters for both area under the curve (AUC) and maximum concentration (Cmax).[2] For products with non-traditional pharmacokinetics, alternative methods such as a pharmacological endpoint or clinical endpoint may serve to demonstrate bioequivalence.

Bioequivalence by Pharmacokinetics example

To better illustrate the difference between demonstrating bioequivalence from pharmacokinetic studies versus a product biowaiver, it is helpful to look at specific examples. Although many examples exist, the following comparison is for the approvals of 2 products (Loncor® and Norfenicol®) which had the same reference product, Nuflor®.

The contents for each product are shown in Table 1. This information was taken from the FOI documents for each product.[6,7] As demonstrated in the table, Loncor qualified for a biowaiver because the ingredient list (both active and inactive) was identical. Whereas Norfenicol was required to demonstrate

bioequivalence through pharmacokinetic studies as the FDA determined that the difference in formulation could potentially lead to a difference in product activity and therefore required submission of evidence that the pharmacokinetic parameters of AUC and Cmax are bioequivalent to the pioneer product Nuflor. The tolerance for variation around these pharmacokinetic parameters is very clearly defined and requires that the tolerance for the range of the new products confidence interval to fall within 80% and 125% of the original product.

While this may at first seem like a wide range, an understanding of the individual animal variation in pharmacokinetic parameters will quickly lead to the conclusion that these are, in fact, fairly reasonable limitations. This process allows reasonable standards to be set to limit product variation while still allowing the manufacture and approval development of generic products. A graphical example of the bioequivalence data from the Norfenicol approval is demonstrated in Figure 2. Because the confidence interval for the pioneer product was

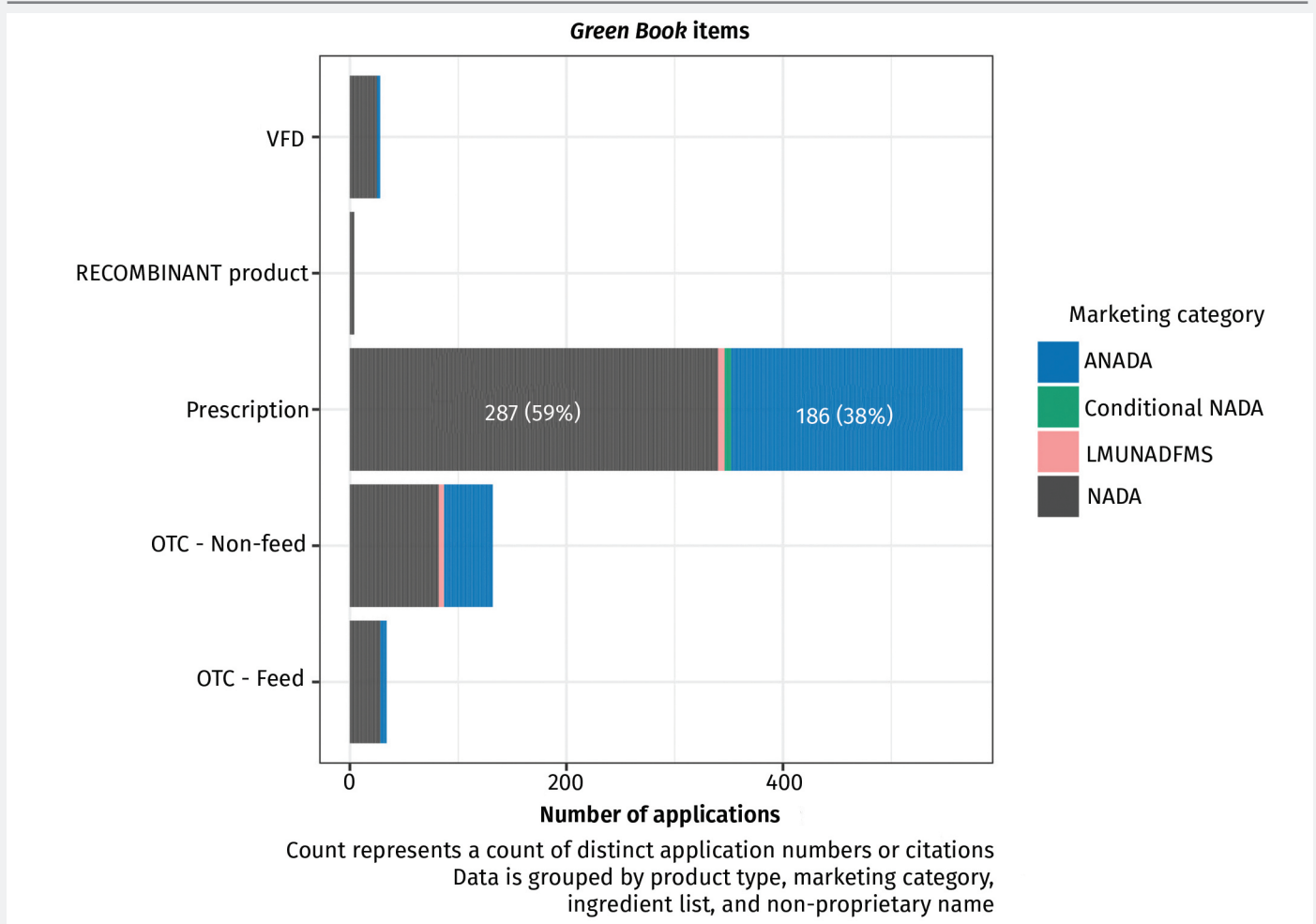**Figure 1:** FDA-approved products from the electronic *Green Book*.

Count represents a count of distinct application numbers or citations
Data is grouped by product type, marketing category, ingredient list, and non-proprietary name

Table 1: Comparison for the approvals of Loncor® and Norfenicol® which had the same reference product, Nuflor®.

	Each ml contains . . .		
	BioEquivalence by Biowaiver	*Pioneer*	*BioEquivalence by PK*
	Loncor® 300	**Nuflor®**	**Norfenicol®**
Florfenicol	300 mg	300 mg	300 mg
N-Methyl-2-pyrrolidone (NMP)	250 mg	250 mg	
propylene glycol	150 mg	150 mg	
polyethylene glycol	qs	qs	
pyrrolidone			250 mg
glycerol formal			qs

not published in the FOI, it is not included in the graphic, but it would also have to fall within the shaded grey region indicating 80-125% of the original mean.

While there are other examples of some generic products being approved as biowaivers and others demonstrating bioequivalence by pharmacokinetics (i.e., oxytetracycline, ceftiofur), most generic approvals seek a biowaiver as the approval method since it is the least costly route to approval.[4] All currently available generic products for both enrofloxacin and tulathromycin were approved by biowaivers.

Green Book products

The electronic *Green Book* is published by the FDA and lists "animal products that have been manufactured, prepared, propagated, compounded, or processed by registered establishments for commercial distribution." [4] Exploration of this list demonstrates that there are a wide range of products and approval types (Figure 3).

While a large proportion of the book lists unapproved products, many of these products (such as lidocaine) are essential to veterinary medicine. The products for which we have a robust approval process include those with a NADA or ANADA. Of these approved products approximately 38% are abbreviated approvals, commonly known as "generics" (Figure 1).

There are 2 additional categories of approval which are "conditional NADA" and LMUNADFMS (legally marketed unapproved new animal drug for minor species). These approval processes are less robust than those for NADA or ANADA. However, they provide means for products reaching the market at a much lower cost and/or allow products to be used for label indications where full approval may never be economically feasible.

Objective observations and contextual data

Discussion of the drug approval process provides a starting point for understanding what evidence exists for the safety and effectiveness of these products in the real world. However, data driven clinical observations within the context of our livestock systems are also important. How do we make objective observations and encourage our clients to do the same? As data becomes more available, our profession must be setting an example of how it should be utilized. While not all situations where we make therapeutic decisions have usable associated data, some do. As our profession moves forward making therapeutic recommendations, it is important that we help ourselves and our clients put our clinical observations within their appropriate context.

Just as the FDA approval process provides a starting point for evidence that a product "works", Donald Wheeler's book *Understanding Variation, the Key to Managing Chaos* provides a sound starting point for how we should utilize clinical data.[8] "*No data have meaning apart from their context*" – Donald Wheeler

Wheeler goes on to state that when this principal is properly applied:

- Trust no one who cannot, or will not, provide the context for their figures
- Stop reporting comparisons between pairs of values except as a part of a broader comparison
- Start using graphs to present current values in context

So, what does this look like from a clinical pharmacology perspective? For farms with greater than 100 treatment events per month, can you demonstrate the trend in therapeutic outcomes for any common disease over the last 3 years? If this information is not at your fingertips, there is plenty of room for our profession to improve the way in which data contributes to our therapeutic decisions. This does not mean that each and every person needs to spend the majority of their time staring at data on a computer screen. On the contrary, it means that we need efficient systems for analyzing data and reporting data back in an efficient format, so that those with appropriate contextual knowledge (boots on the ground) can actually do something with that information.

For those who dislike working with data and calculations and prefer interacting with real cows and humans, fantastic! You are the ones who can truly provide the context for the therapeutic data generated by farm management systems. Knowing the data context requires knowing:

- Who collected it
- How was it collected
- When was it collected
- Where was it collected
- What data was collected
- The formula for calculations
- The formula for detecting change over time

The monitoring of therapeutic outcomes in clinical scenarios is also an important piece of clinical pharmacology evidence. We have an opportunity as a veterinary profession to become more efficient at helping our clients differentiate signal from noise and understand what therapeutic efficacy trends they should expect within their livestock systems.

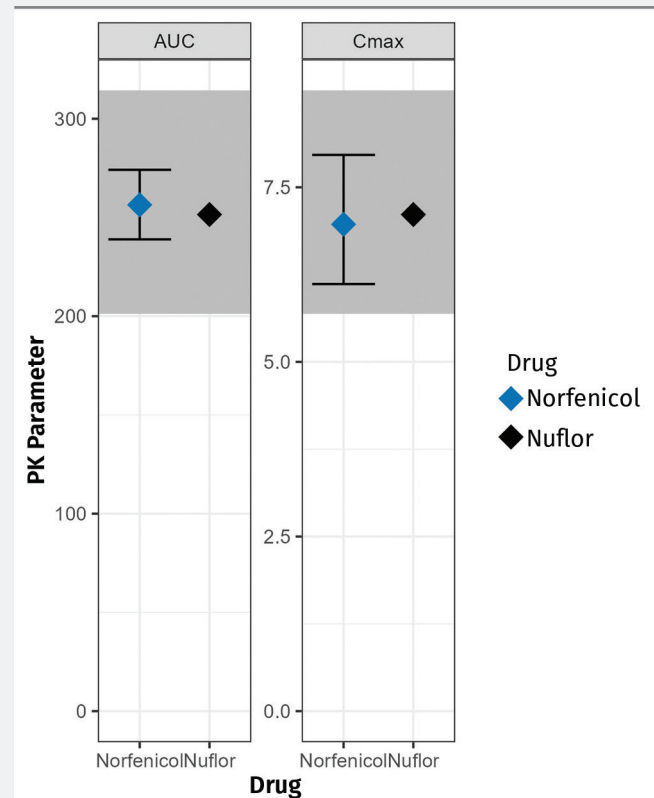**Figure 2:** Graphic representation of data from the Norfenicol® FOI bioequivalence study from FOI data.[6,7]
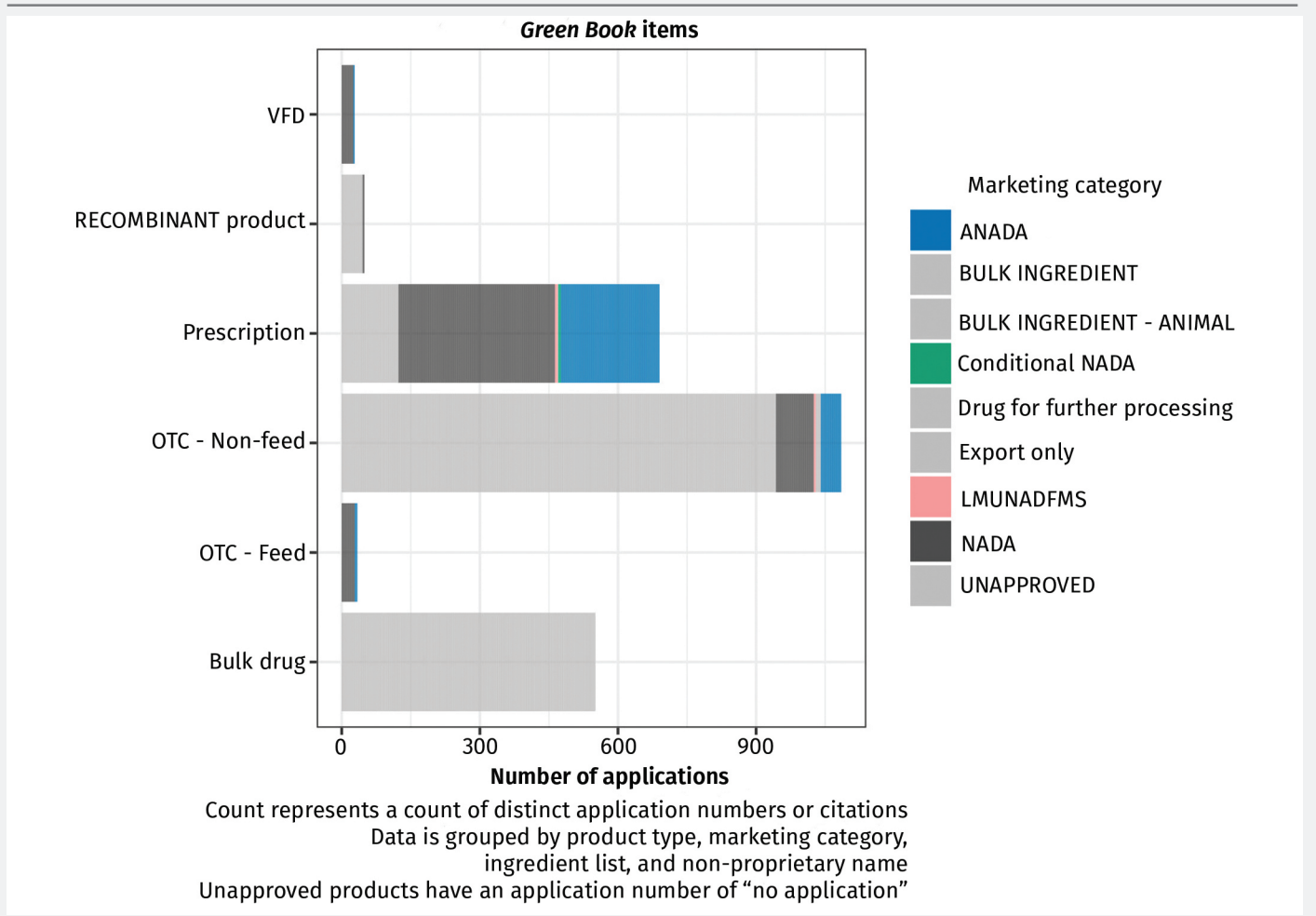
Figure 3: Electronic *Green Book* items.

Count represents a count of distinct application numbers or citations
Data is grouped by product type, marketing category,
ingredient list, and non-proprietary name
Unapproved products have an application number of "no application"

Summary

Within clinical practice it is necessary to utilize FDA approved novel products, FDA-approved generic products, and non-FDA-approved products. Each of these products have their place, and livestock producers should be able to rely on their veterinarians to have a full understanding of the efficacy and safety evidence behind the products they are using. Routine monitoring of therapeutic outcomes can also be informative in systems where this data exists. Evidence from well designed robust clinical trials is the most useful evidence for direct application to clinical therapeutic decisions.

Do not confuse the 2 questions of "Does the DRUG work" and "Did the TREATMENT work". Evidence for "Does the DRUG work" comes from carefully controlled studies designed to answer this question (often approval studies). Evidence for "Did the TREATMENT work" comes from real world observational data. It is tremendously confounded by things like case definition, environment, cattle source, etc. It is still an important question, but a fundamentally different one.

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