DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAY 7 2008

Re: Cydectin
Docket No.: 2004E-0040

Christopher N. Sipes
Covington & Burling LLP
1201 Pennsylvania Avenue N.W.
Washington, D.C. 2004-2401

RE: Patent Term Extension for Wyeth Holdings Corporation, U.S. Patent No. 4,916,154, Cydectin, Request for Revision of Regulatory Review Period

Dear Mr. Sipes:

This letter is in response to your November 20, 2006, request on behalf of Wyeth Holdings Corporation (Wyeth) for reconsideration and revision of the regulatory review period for Cydectin (moxidectin), U.S. Patent No. 4,916,154, filed by American Cyanamid Company (ACC), now Wyeth, under 35 U.S.C. § 156 et seq. In the September 20, 2006, issue of the *Federal Register* (71 Fed. Reg. 54993), the Food and Drug Administration (FDA) published its determination of this product's regulatory review period for purposes of patent term extension, as required under 35 U.S.C. § 156(d)(2)(A). As described below, FDA upholds the determination of the regulatory review period as published.

I. Your Request

You believe the date FDA determined as the date the Cydectin application was submitted is incorrect and you request a correction and recalculation of the regulatory review period for the following reasons:

- You believe the date the application was initially submitted with respect to the animal drug product under section 512(b) of the Federal Food, Drug, and Cosmetic Act (the Act) was August 8, 1995, the date ACC submitted the initial component of the new animal drug application (NADA).
- You believe the approval phase of the regulatory review period begins when the new animal drug applicant has submitted enough information for FDA to begin its review.
- You believe that Congress intended that an animal drug application is "initially submitted" when the applicant provides sufficient information for the Agency to commence review for approval, even if the application is not yet complete or filed. You believe a phased review application is *initially submitted* long before the formal filing of an administrative NADA.
- You describe the phased review process for animal drug applicants as an alternative method of review for applications to market animal drugs. In your description, under phased review, an applicant may submit data or information in support of a technical section, or may submit a complete technical section of the NADA separately from other sections. If the data submitted in support of a technical section are complete, you state

that the Center for Veterinary Medicine (CVM) will begin review and will issue a complete letter for the section in question. After CVM has issued a complete letter for each technical section, the applicant files an administrative NADA, including the communications from FDA to the applicant advising that the data submitted in support of each component are acceptable. A final decision approving an application is issued only after the applicant files an administrative NADA.

- You state that ACC submitted an investigational new animal drug application (INAD) 6736 for moxidectin in March 1990 and submitted each component of the Cydectin marketing application for FDA review under the phased review process. You state that the components were submitted to INAD 6736.
- You believe from the statement in the 10-page March 26, 1996, "incomplete letter" from CVM that CVM engaged in substantive review of the information submitted on August 8, 1995.
- You believe that using January 13, 1998, as the date of initial submission is implausible, implying that FDA completed the entire review of the Cydectin application in a 15-day time span.
- You believe for phased review applications that determination of the initially submitted date as the date that the administrative NADA is filed is inconsistent with Congressional intent. You state Congress explicitly distinguished between submission of enough information to allow Agency review to begin and the formal step of filing, which occurs only after an application is complete.
- You believe re-defining the approval phase to encompass only the short period needed to approve an administrative NADA (for Cydectin this is just 15 days) deprives the applicant of full credit for the time consumed by FDA's review.
- You believe the Cydectin case is distinguishable from other previous FDA determinations of an initially submitted date at the point when the applicant formally submits a complete application because the previous cases did not involve a rolling submission that triggered commencement of FDA review.
- You believe ACC was diligent in submitting information for review of its product, submitting additional technical sections within a few months of the August 8, 1995, submission.

II. FDA Response

A. Regulatory Review Period

For purposes of patent term extension, a regulatory review period is the sum of two periods of time: a testing phase and an approval phase. As clarified in Title 21 Code of Federal Regulations (21 CFR) § 60.22(d)(1), for animal drug products, the testing phase begins on the date a major health or environmental effects test is begun or the date on which the Agency acknowledges the filing of a notice of claimed investigational exemption for a new animal drug, whichever is earlier, and ends on the date a marketing application under section 512 of the Act is initially submitted to FDA. The approval phase begins on the date a marketing application under section 512 of the Act is initially submitted to FDA and ends on the date the application is

approved (21 CFR § 60.22(d)(2)). Although only a portion of a regulatory review period may count toward the actual amount of extension that the Director of Patents and Trademarks may award (for example, half the testing phase must be subtracted, as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for an animal drug product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(4)(B).

B. Administrative NADAs and Phased Review

According to the *Center for Veterinary Medicine Document and Submission Information – An Update, April 1995* (CVM Update) summary of the Phased Data Review Policy,[1] "each submission should contain data supporting only one technical section. Data supporting different technical sections of the NADA may be submitted concurrently, but because each will be assigned to the applicable review division, separate submissions are required. . . . The submission should also clearly reference the INAD . . ." This is followed by "Each data submission is filed in the INAD file." In addition, "the sponsor may submit an NADA at anytime, but the NADA must address all technical sections of the NADA or CVM will refuse to file the application. If any technical sections, or studies, have been previously reviewed by the Center under the phased review policy, the sponsor's data and CVM's decision may be incorporated in to the NADA by reference to those submission(s) and the Center's response letter(s)."

As further clarified in the FDA draft guidance, *The Administrative New Animal Drug Application Process,* (the Administrative NADA Guidance), November 6, 2002,[2]

> An administrative NADA is a new animal drug application that is submitted after all of the technical sections that fulfill the requirements for the approval of the new animal drug under 21 Code of Federal Regulations (CFR) 514.1 have been reviewed by CVM and CVM has issued a technical section complete letter for each of those technical sections.
> (page 3)

> A sponsor may submit data or information in support of a technical section, or may submit a complete technical section, of the NADA for review during the investigation of the new animal drug, i.e. for phased review. . . Phasing of NADA submissions is a voluntary program.
> (page 3)

In addition, the Administrative NADA Guidance addresses the potential impact of submission of an administrative NADA on patent term extensions.

> In deciding whether to seek approval of a new animal drug under phased review or under the traditional review process by submitting all data together, a sponsor

[1] Page 16 of the CVM Update.
[2] Available on the Internet at www.fda.gov/cvm/Guidance/dguide132.pdf.

> should consider all advantages and disadvantages of each mechanism for approval before submitting data for CVM's review. For example, a sponsor should consider whether seeking approval of a new animal drug under phased review will affect the extension of a patent term. See the discussion in section V. of this guidance.
> (page 3, footnote 2)

> . . .If a sponsor exercises the option to use the phased review process: Submissions relating to technical sections should be submitted during the investigation of the new animal drug and filed in an INAD file established by CVM for the new animal drug.
> (page 3)

The Administrative NADA Guidance also clearly addresses, for patent term extension purposes, the dates that define the regulatory review periods.

> Section 512(c)(1) of the Act requires FDA to approve or not approve an NADA within 180 days, . . . after the filing of an application. . . . If the data are submitted as part of the phased review process, CVM intends to consider the NADA submitted when it receives an Administrative NADA, because it is at this point that the agency should have all the elements required by 21 Code of Federal Regulations Part 514.1.
> (page 7)

> . . . In summary, however, the regulatory review period is divided into two time periods. The first period (sometimes called the investigational period) begins when the sponsor submits a request to CVM to establish an INAD file. . . The second period (the approval period) begins with submission of the NADA and ends when the application is approved. 35 U.S.C. § 156(g)(4)(B). Subject to certain important limitations, a patent may be extended for a time roughly equal to the second period plus one half the first time period. 35 U.S.C. § 156(c)(2). Because FDA intends that the time it takes to approve an application that qualifies as an Administrative NADA usually will be shorter than the time it takes to approve a traditional NADA, a new animal drug that was the subject of an Administrative NADA is likely, in most cases, to receive a shorter patent term extension than it would have received had it been the subject of a traditional NADA.
> (page 7-8)

C. When Was The Cydectin NADA Initially Submitted Under Section 512?

As noted above, the approval phase for new animal drug products begins the date the new animal drug *application* is initially submitted under section 512 of the Act. You argue that the August 8,

1995, date is the date the *application* was initially submitted, because FDA could begin at least a partial review of what became the first module of the administrative NADA. We disagree.

First, for phased review applications, it is FDA's position that the approval phase for purposes of patent term extension begins when the marketing application is complete, including *all* technical sections and the CVM complete letters. This correlates to the "fast track" and "rolling review" of human drug applications in that applications submitted under those programs are not considered initially submitted until all required technical information is addressed and available for FDA decision making to commence. Although this approach can result in a very short approval phase, it is most consistent with the idea that alternative drug development and review approaches are intended to permit the applicant to respond to FDA input as the application is developed, making FDA's review more efficient, and shortening the time required for review of the application.

Second, the technical sections of the administrative NADA are submitted for FDA review not to the NADA, but to the INAD. Regulatory review of the components is conducted under the first investigational phase of the regulatory review period allowing for review of the data at the time most appropriate and productive in the drug development process. Consequently, for the purposes of patent term extension, the approval phase of the regulatory review period for phased review new animal drug products begins when the administrative NADA, including all of the technical sections required for approval of the new animal drug under 21 CFR 514.1 and the corresponding technical section complete letters, is submitted under section 512 of the Act.

A review of FDA records reveals that the date of FDA's official acknowledgment letter assigning a number to the collection of all the technical sections and the CVM complete letters in administrative NADA 141-099 for Cydectin was January 13, 1998. FDA reiterates that January 13, 1998, the date of FDA receipt of the complete application, is the initial submission date of the application and the beginning of the approval phase of the regulatory review period for patent term extension.

Consequently, the regulatory review period for Cydectin as published in the September 20, 2006, *Federal Register* is correct, and your request for revision and recalculation of the regulatory review period is denied.

Please let me know if we can be of further assistance.

Sincerely yours,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

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Revision: 2/22/2008, 3/27/2008
Edited: S. O'Malley 4/11/2008
Revised: B. Friedman 4/15/2008
Reviewed: J. Axelrad