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November 20, 2006

Dockets Management Branch
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fisher Lane, Room 1061
Rockville, MD 20852

Re: Request for Revision of Regulatory Review Period
CYDECTIN
Docket No. 2004E-0040

Dear Sir or Madam:

Wyeth Holdings Corporation, formerly known as American Cyanamid Company, on behalf of its Fort Dodge Animal Health business, through undersigned counsel, hereby requests reconsideration and revision of the Determination of Regulatory Review Period published in the Federal Register on September 20, 2006 (Fed. Reg. Vol. 71, No. 182 at 54993-94). In accordance with 21 C.F.R. § 60.24(a), the following information is provided:

(1) The Type of Action Requested

For the reasons stated below, Applicant respectfully requests that the "date the application was initially submitted with respect to the animal drug product under section 512(b) of the act" be corrected from January 13, 1998, the date provided in the Federal Register notice, to August 8, 1995. Applicant also requests that the agency recalculate the "regulatory review period" accordingly.

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(2) The Identity of the Product

CYDECTIN® moxidectin 0.5% Pour-On for Cattle ("Cydectin") (NADA 141-099), the product that is the subject of the regulatory review period determination, is marketed and sold by the Fort Dodge Animal Health business.

(3) The Identity of the Applicant

American Cyanamid Company ("American Cyanamid") was the initial Applicant on the Request for Extension of Patent Term. American Cyanamid, by virtue of a name change in December 2002, is now known as Wyeth Holdings Corporation.

(4) The FDA Docket Number

The FDA Docket Number for this Determination of Regulatory Review Period is 2004E-0040.

(5) The Basis for the Request for Revision, Including Any Documentary Evidence

American Cyanamid submitted the initial component of the animal drug marketing application for CYDECTIN® moxidectin 0.5% Pour-On for Cattle on August 8, 1995. The Center for Veterinary Medicine ("CVM") of the Food and Drug Administration ("FDA") began reviewing that information shortly thereafter. Therefore, August 8, 1995 is the date on which the application was "initially submitted" to FDA for purposes of the Generic Animal Drug and Patent Term Restoration Act of 1988

("GAD/PTR Act").[1] As shown below, this conclusion is consistent with the statute, Congressional intent, and FDA's implementing regulations.

Documentary evidence supporting this Request for Revision is provided in Exhibits A through D hereto. In addition, the discussion below includes references to documents in FDA's files.

I. LEGISLATIVE FRAMEWORK

A. The Statute Provides That the Approval Phase Begins When an Application Is "Initially Submitted."

The GAD/PTR Act brought animal drugs and veterinary biologicals within the statutory framework Congress had previously established in the Drug Price Competition and Patent Term Restoration Act of 1984 ("DPC/PTR Act").[2] Congress recognized that "animal drug innovators typically lose years of patent protection because of FDA's scientific testing requirements and regulatory review."[3] Congress intended the GAD/PTR Act to stimulate research and development of animal drugs by restoring patent life lost during FDA-required testing and review, thereby allowing developers of new animal drugs to recoup more of their research and development costs.[4]

The GAD/PTR Act provides that the term of a patent for an animal drug product may be extended for up to five years if, prior to marketing, the product was

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1 Pub. L. No. 100-670, 102 Stat. 3971 (1988).

2 Pub. L. No. 98-417, 98 Stat. 1585 (1984).

3 H. R. Rep. No. 100-972, pt. 1, at 3 (1988); *see also* H. R. Rep. No. 100-972, pt. 2, at 16 (1988).

4 134 Cong. Rec. 30272 (1988) (statement of Sen. Hatch); 134 Cong. Rec. 30560 (1988) (statement of Rep. Waxman).

subject to regulatory review by FDA.[5] It is necessary to calculate the "regulatory review period" to determine the length of the patent term extension. For a new animal drug, this period covers time consumed by two phases that typically occur during the life of the patent and substantially reduce the time the drug may be marketed while subject to patent protection. The first phase (the "testing phase") begins on the date "an exemption under subsection (j) of section 512 became effective for the approved new animal drug product" and ends "on the date an application was *initially submitted* for such animal drug product under section 512."[6] The second phase (the "approval phase") begins "on the date the application was *initially submitted* for the approved animal drug product under subsection (b) of section 512" and ends "on the date such application was approved under such section."[7]

Congress was particularly concerned with the restoration of patent rights to make up for time lost during FDA's review of an application. While Congress

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5 Pub. L. No. 100-670, 102 Stat. 3971 (1988).

6 35 U.S.C. § 156(g)(4)(B)(i) (emphasis added). FDA regulations refer to this period as the "testing phase." 21 C.F.R. § 60.22. The regulations explain that "[t]he testing phase begins on the date . . . on which the agency acknowledges the filing of a notice of claimed investigational exemption for a new animal drug . . . and ends on the date a marketing application under section 512 of the Act is initially submitted to FDA." 21 C.F.R. § 60.22(d)(1).

The patent term may be extended by one-half of the time an animal drug is in the testing phase. *See* 35 U.S.C. § 156(c)(2).

7 35 U.S.C. § 156(g)(4)(B)(ii) (emphasis added). FDA regulations refer to this period as the "approval phase." 21 C.F.R. § 60.22.

The patent term may be extended for as many days as the animal drug was in the approval phase. For a patent issued after the enactment of the GAD/PTR Act, however, the period of extension may not exceed five years. *See* 35 U.S.C. § 156(g)(6)(A). In addition, the patent term may not extend beyond 14 years after the date of approval. *See* 35 U.S.C. § 156(c)(3).

provided for only 50 percent restoration of time spent during the testing phase, it specified that full credit be given once the approval phase began, when FDA review was ongoing. Hence, it began the full-credit approval phase with the "initial" submission of the marketing application, without regard to whether testing under the investigational exemption was still proceeding.

B. The Legislative History Makes Clear That an Application Is "Initially Submitted" When FDA Has Sufficient Information to Commence Review.

Congress intended that, for purposes of computing restoration of patent life, the approval phase would begin at the point when FDA has received enough information to begin review. The legislative history shows that Congress deliberately chose the words "initially submitted" to identify the commencement of the approval phase, explicitly distinguishing that moment from a later point in time when an application is considered "filed." The House Report accompanying the DPC/PTR Act notes that in the definition of the "regulatory review period,"

> the term "initially submitted" is used to describe the point in time when the testing phase is considered to be completed and the agency approval phase to have begun. This term is used instead of the term "filed," because an application is often not considered to be filed, *even though agency review has begun*, until the agency has determined that no other information is needed and a decision on the application can be made. For purposes of determining the regulatory review period and its component periods, an application for agency review is considered to be "initially submitted" if the applicant has made a deliberate effort to submit an application containing all information necessary for agency review to begin. The Committee recognizes that the agency receiving the application might decide it needs additional information or other changes in the application. *As long as the application was complete enough so*

that agency action could be commenced, it would be considered to be "initially submitted."[8]

Thus, the approval phase begins when the new animal drug applicant has submitted enough information for FDA to begin its review. This makes sense because the amount of patent life consumed by FDA's review of the marketing application depends on when FDA *begins* its review of the application. Importantly, the House Report states that an application is considered "initially submitted" when the materials submitted are complete enough that the agency can commence review, *not* when an applicant has submitted all components of the application. Congress plainly intended that an application would be considered "initially submitted" when FDA has enough information to begin the review process, even if the application is not yet complete or "filed."

II. REGULATORY FRAMEWORK

A. FDA Regulations State That an Animal Drug Application Is "Initially Submitted" When the Applicant Provides Sufficient Information for the Agency to Commence Review.

FDA's regulations implementing the GAD/PTR Act are consistent with the language and legislative history of the statute, providing that the approval phase begins when FDA has sufficient information to commence review of the application. The

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[8] H. R. Rep. No. 98-857, pt. 1, at 44 (1984) (emphasis added). Congress first used the words "initially submitted" in defining the "regulatory review period" in the DPC/PTR Act, which predated the GAD/PTR Act by four years. The Congressional Reports accompanying the GAD/PTR Act do not further explain the words "initially submitted" as they are used in the definition of "regulatory review period." However, the discussion of the DPC/PTR Act is relevant here because the GAD/PTR Act "simply makes the additions to sections 156 and 271 necessary to include animal drugs and veterinary biologicals within the existing statutory framework." H. R. Rep. No. 100-972, pt. 1, at 8; H. R. Rep. No. 100-972, pt. 2, at 20.

regulations state that "[t]he 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."[9] They go on to explain that, "[f]or purposes of determining the regulatory review period for any product, a marketing application . . . is *initially submitted* on the date it contains sufficient information *to allow FDA to commence review* of the application."[10] Thus, if an applicant has provided FDA with sufficient information regarding a substantial element of an application, so that the agency is in a position to commence review of the application, the approval phase begins.

B. Animal Drug Applicants May Elect a Phased Review Process.

In the case of animal drugs, the timing of FDA review will depend on the choice of review process. FDA has two independent tracks for approval of a New Animal Drug Application ("NADA"). Under its traditional review process, CVM will not accept and review separate submissions of individual components of a NADA.[11] Rather, the agency begins review only upon receipt of the entire NADA.

An alternative method of review for applications to market animal drugs is provided, where applicants may elect to have the agency conduct a "phased review" of a NADA. Phased review requires submission of the same technical sections required to support a traditional NADA. Under phased review, however, an applicant may submit data or information in support of a technical section, or may submit a complete technical

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9 21 C.F.R. § 60.22(d)(2) (emphasis added).

10 21 C.F.R. § 60.22(f) (emphasis added).

11 *See* 21 C.F.R. § 514.1(b).

section of the NADA, separately from the other sections.[12] CVM will begin to review this section even if other sections have not yet been submitted. CVM will notify the applicant in writing of its conclusions regarding the data submitted with a particular technical section. If the data submitted in support of a technical section are complete, CVM will issue a "complete letter" for the section in question. After CVM has issued such a letter for each technical section, the applicant files an "Administrative NADA." This "Administrative NADA" includes the communications from FDA to the applicant advising that the data submitted in support of each component are acceptable, *i.e.*, a full set of "complete letters."[13] A final decision approving an application is issued only after the applicant files an Administrative NADA (*i.e.*, after CVM has issued a "complete letter" for every section).

C. A Phased Review Application Is "Initially Submitted" Long Before Formal Filing of the Administrative NADA.

When an animal drug application is submitted under the phased review process, the application is "initially submitted" long before the filing of the Administrative NADA. FDA begins its review with the submission of the first technical section supporting an application, rather than waiting until all sections have been

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[12] *See* FDA, Center for Veterinary Medicine, Policy and Procedures Manual Guide 1240.3040 (1989). (A copy of this portion of the guide is attached as Exhibit A hereto.) In the phased review process FDA directs applicants to file the technical sections of the application in the existing Investigational New Animal Drug File ("INAD"), rather than under a NADA docket number. *See* FDA, Center for Veterinary Medicine, Document and Submission Information - An Update (April 1995), p. 1. (Relevant pages of this April 1995 document are attached as Exhibit B hereto.) The "complete letters" reflecting review of those sections ultimately become part of the NADA docket. *See id.* at 17.

[13] *See* FDA, Center for Veterinary Medicine, The Administrative New Animal Drug Application Process: Draft Guidance #132 (Nov. 6, 2002), p. 6. (A copy of Draft Guidance #132 is attached as Exhibit C hereto.)

submitted. So long as the first submission contains sufficient information for CVM to begin a meaningful review, the application has been "initially submitted" and the approval process has begun.

CVM itself describes the process in these terms. The agency's guidance documents state that under the phased review process CVM will begin reviewing an animal drug marketing application upon the submission of a reviewable component required under 21 C.F.R. §514.1.[14] Its April 1995 update to Document and Submission Information states:

> [CVM] remains *extremely* committed to the concept of reviewing data at the most appropriate and productive times in the drug development process and CVM will continue to accept data for evaluation outside the strict structure of "all in, all out" of the conventional NADA.[15]

Thus, in the phased review process, substantive review does not await the submission of all sections of the application, nor does it await a formal "filing" of the Administrative NADA. That formal act of filing an Administrative NADA occurs only after the agency's substantive review is essentially complete.[16]

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[14] Exhibit C, Draft Guidance # 132, p. 3; *see also* FDA, Center for Veterinary Medicine, Content and Format of Effectiveness and Target Animal Safety Technical Sections and Final Study Reports for Submission to the Division of Therapeutic Drugs for Non-Food Animals: Guidance #104 (July 10, 2001), p. 5. (A copy of relevant pages of Guidance #104 is attached as Exhibit D hereto.)

[15] Exhibit B, Document and Submission Information -- An Update, p. 1 (emphasis in original).

[16] *See* Exhibit C, Draft Guidance #132, p. 7 ("If an application meets the definition of an Administrative NADA, the review should take fewer than 180 days because the *review of the individual sections of the application has already been completed.*") (emphasis added).

Any conclusion that an application handled through the phased review process has been "initially submitted" only when all sections of the application have been submitted and reviewed and the Administrative NADA has been filed would be wholly inconsistent with Congressional intent. Congress wanted to restore the full amount of time consumed by FDA review of a marketing application. As discussed above, in explaining its choice of the words "initially submitted" to define the beginning of the approval phase, Congress explicitly distinguished between submission of enough information to allow agency review to begin and the formal step of "filing," which may occur only after an application is complete. Congress made clear that it was choosing the earlier point as the beginning of the approval phase. Under the phased review process, all of this review (consuming several years in this case) occurs before filing of the Administrative NADA. Re-defining the approval phase to encompass only the short period needed to approve an Administrative NADA (just 15 days here) would deprive the applicant of full credit for the time consumed by FDA's review, contrary to Congress's intent.

Although in two cases FDA has concluded that a new human drug application was "initially submitted" only at the point when the applicant formally submitted a complete application,[17] this case is clearly distinguishable. These other cases

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[17] In Docket No. 91E-0491, FDA concluded that an "incomplete application" submitted by Sankyo and Bristol-Myers Squibb did not contain sufficient information to permit FDA to commence review, despite the fact that FDA staff had made inquiries about information in the application. The agency concluded that the application was not "initially submitted" where the submission did not include all information the agency had required in presubmission communications with the applicant. *See* Letter from Stuart L. Nightingale, M.D., Associate Commissioner for Health Affairs, FDA, to Terry Coleman, Esq., Fox, Bennett & Turner (March 1, 1994), *available in* FDA Docket No. 91E-0491.

did not involve a rolling submission that triggered commencement of FDA review. In fact, FDA's reasoning in Docket No. 91E-0491 supports Applicant's argument here. In that docket, FDA apparently acknowledged that an application could be "initially submitted" before it was formally filed. The critical fact in that case was that the applicant there had not submitted enough information for FDA to begin its review.

As described above, when an applicant elects phased review, the agency's review begins long before an application is complete. FDA can comply with Congress's intent to grant full credit for the period consumed by agency review only if it finds that the application is "initially submitted" when the applicant submits the first round of information in support of the application.

III. CALCULATION OF THE REGULATORY REVIEW PERIOD FOR CYDECTIN PATENT EXTENSION

The patent for which extension is sought is Patent No. 4,916,154, issued on April 10, 1990. In March 1990 American Cyanamid requested establishment of INAD 6736 to investigate the use of its proprietary endectocide compound, moxidectin, when administered topically to cattle as the active component of a novel pour-on formulation. Moxidectin acts to rid the cow of internal parasites, resulting in a healthier animal that processes its feed more efficiently (producing greater weight gain in beef cattle and more milk production in dairy cattle). It is approved for use by "organic farmers," due to its environmental friendliness towards beneficial insect populations.

See also Aktiebolaget Astra v. Lehman, 71 F.3d 1578, 1578-79 (Fed. Cir. 1995) (noting FDA's decision that an "early" submission of information did not start the review period clock and that Astra's approval stage began only when the company filed the last component of its NDA).

In August 1995, American Cyanamid began the process of seeking approval for the marketing of its Cydectin moxidectin product. The Fort Dodge Animal Health business eventually assumed responsibility for this process. FDA granted approval of the marketing application on January 28, 1998.

A. FDA Used the Phased Review Process for the Cydectin Marketing Application.

FDA reviewed the marketing application for Cydectin under the phased review process. Each component of the application was submitted separately, referencing the phased review procedure. The agency issued separate "complete letters" after reviewing each individual component. The following table lists the dates on which each component of the Cydectin marketing application was submitted for phased review and the date CVM issued the "complete letter" for that component.[18]

Component	Submission Date	Date of "Complete Letter"
Residue Chemistry and Regulatory Methods	August 8, 1995	December 10, 1997
Target Animal Safety	December 15, 1995	June 22, 1996
Manufacturing Chemistry	December 21, 1995	September 17, 1996
Effectiveness	January 16, 1996	November 4, 1997
Public Safety/Food Safety	June 7, 1996	January 13, 1998
Environmental Safety	August 14, 1996 Amended on June 13, 1997	December 23, 1997

[18] The components of the application were submitted in INAD Docket No. 6736. Ultimately the "complete letters" were included as part of the Administrative NADA, Docket No. 141-099.

On January 13, 1998, upon receipt of the "complete letter" for the final components of the application, Fort Dodge submitted its Administrative NADA for Cydectin, citing all the "complete letters" FDA had previously issued for components of the application. On January 14, 1998, the agency issued an acknowledgment letter for the Administrative NADA, and on January 28, 1998, just 15 days after submission of the Administrative NADA, FDA issued the approval letter for Cydectin.

B. The Application for Cydectin Was "Initially Submitted" on August 8, 1995.

The marketing application for Cydectin was "initially submitted" to FDA on August 8, 1995, when the Residue Chemistry component of the application was submitted to the agency. At that point there was "sufficient information to allow FDA to commence review of the application."[19] The cover letter that accompanied the submission stated that the submission provided "all information and data comprising the 'Residue Chemistry and Regulatory Methods' technical section for review and final acceptance by CVM under the Phased Review Submission Policy."[20] The submission contained four sets of information, covering the subjects of total metabolism in target animal, comparative metabolism in rodents, tissue residue depletion studies, and analytical methods and method validations. A total of 4,790 pages (primarily study data) accompanied the cover letter.

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[19] 21 C.F.R. § 60.22(f).

[20] The cover letter and table of contents of the August 8, 1995 submission, as well as the extensive data provided with the letter, are part of CVM's files, as are the other documents cited below.

After receiving this initial component of the application, FDA began its substantive review. On March 26, 1996, CVM issued a 10-page "incomplete letter," advising that more information was needed in connection with this component. That letter confirms that CVM had been engaging in a substantive review of the information submitted on August 8, 1995. On page 1 of the letter, the Director, Division of Chemistry, Office of New Animal Drug Evaluation of CVM, stated: "*We have reviewed your submissions* and have extensive comments to pass on to you."[21] The letter went on to state:

> *You submitted an extensive amount of data* that is intended to fulfill our residue chemistry requirements. We concluded that you did an excellent job of reporting the claimed pivotal studies. This conclusion has been borne out by the audit reports, which have noted only minor discrepancies. Thus, there are no substantive findings that would invalidate any study for procedural reasons. *We proceeded with our review*, therefore, focusing on whether the data met established policies and adequately addressed outstanding residue chemistry questions.[22]

While the letter concluded that more work was needed to satisfy the requirements for the Residue Chemistry section, CVM expressed satisfaction with other aspects of the submission.

The statements in the March 26 letter from CVM make it clear that the August 8 submission contained enough information to permit review to begin and that CVM staff had, in fact, engaged in an in-depth review of the data submitted. In these

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[21] Letter from Nicholas E. Weber, Ph.D., Director, Division of Chemistry, Office of New Animal Drug Evaluation, Center for Veterinary Medicine, to Dr. Robert E. Pollet, Director, New Products, Global Animal Regulatory Affairs, American Cyanamid, Mar. 26, 1996, at 1 (emphasis added).

[22] *Id.* at 1-2 (emphasis added).

circumstances, there can be no question that the Cydectin application was "initially submitted" on August 8, 1995, and the approval phase began on that date.

FDA's choice of January 13, 1998, as the date the Cydectin application was "initially submitted" is quite implausible. FDA approved the Administrative NADA on January 28, 1998. Thus, under FDA's reasoning, the agency must have conducted its entire review of the Cydectin application, from start to finish, in just 15 days. In view of the complexity of the review process for a new animal drug, this makes no sense. FDA cannot reasonably suggest that the review and approval process spanned a mere 15 days. In fact, as CVM's own correspondence reveals, the substantive review of the various components of the application covered almost two and a half years, when the initial round of information was submitted on August 8, 1995.

FDA's conclusion that the Cydectin application was "initially submitted" on January 13, 1998, the date the Administrative NADA was filed, is inconsistent with FDA's own regulation because the August 8, 1995 filing was sufficient to allow CVM to begin a substantive review of one section required as part of the application. Moreover, FDA's determination disregards Congress's deliberate decision to pick a date different from (and earlier than) the official "filing" date as the beginning of the approval phase, to be certain that applicants would obtain full credit for the time lost as a result of FDA review.

FDA's conclusion that the Cydectin application was "initially submitted" on January 13, 1998 -- just 15 days before the Administrative NADA was approved -- rather than August 8, 1995, has the result of depriving Fort Dodge of full credit for two and a half years of the time when FDA was conducting its review of the various

components of the application. The effect of this determination is that these years will be classified as part of the testing phase, and only half that time is restored to the patent term. This result is directly contrary to Congress's intent that applicants receive full credit for the period of FDA review.

Applicant was clearly diligent in submitting information for review and otherwise pushing the approval process forward. Within a few months of the initial submission, it submitted in quick succession three more sections of the application -- relating to Target Animal Safety, Manufacturing Chemistry, and Effectiveness (submitted on December 15, 1995, December 21, 1995, and January 16, 1996, respectively). CVM issued a "complete letter" for Target Animal Safety on July 22, 1996, and for Manufacturing Chemistry on September 17, 1996. In the meantime, Applicant submitted additional sections, as well as additional information for the sections that CVM had determined to be incomplete. Phased review worked exactly as it should have, and there is no basis for concluding that the Cydectin application was "initially submitted" on any date other than the date when the first component was submitted. FDA should grant full credit for the review and approval period by determining that the application was "initially submitted" on August 8, 1995.

C. The Regulatory Review Period for Cydectin

The investigational new animal drug application for Cydectin became effective on April 5, 1990. As explained above, the marketing application for Cydectin was "initially submitted" to FDA on August 8, 1995. FDA approved the marketing application for Cydectin on January 28, 1998.

The testing phase for Cydectin is the time between the effective date of the investigational new animal drug application and the date the marketing application was "initially submitted" -- a total of 1952 days. The approval phase began when the Applicant "initially submitted" the marketing application and ended on the date that FDA approved the marketing application. Thus, the length of the approval phase for Cydectin was 905 days.

CONCLUSION

For the reasons discussed above, FDA's determination of the regulatory review period for Cydectin is incorrect. The agency should revise the determination to reflect that the application was "initially submitted" on August 8, 1995, and that the approval phase of the regulatory review period began on that date.

Respectfully submitted,

Christopher N. Sipes
Attorney for Wyeth Holdings Corporation