

biological products, the testing phase begins when the exemption to permit the clinical investigations of the biological becomes effective and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the human biological product and continues until FDA grants permission to market the biological product. 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 a human biological product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(1)(B).

FDA recently approved for marketing the human biological product ZEVALIN (CD20 Monoclonal Antibody). ZEVALIN is indicated for treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma, including patients with Rituximab (Rituxan) refractory follicular non-Hodgkin's lymphoma; the therapeutic regimen includes Rituximab, Indium-111 Ibritumomab Tiuxetan, and Yttrium-90 Ibritumomab Tiuxetan. Subsequent to this approval, the Patent and Trademark Office received a patent term restoration application for ZEVALIN (U.S. Patent No. 5,776,456) from IDEC Pharmaceuticals Corp., and the Patent and Trademark Office requested FDA's assistance in determining this patent's eligibility for patent term restoration. In a letter dated February 3, 2003, FDA advised the Patent and Trademark Office that this human biological product had undergone a regulatory review period and that the approval of ZEVALIN represented the first permitted commercial marketing or use of the product. Shortly thereafter, the Patent and Trademark Office requested that FDA determine the product's regulatory review period.

FDA has determined that the applicable regulatory review period for ZEVALIN is 3,363 days. Of this time, 2,887 days occurred during the testing phase of the regulatory review period, while 476 days occurred during the approval phase. These periods of time were derived from the following dates:

1. *The date an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)) became effective:* December 7, 1992. FDA has verified the applicant's claim that the date the investigational new

drug application became effective was on December 7, 1992.

2. *The date the application was initially submitted with respect to the human biological product under section 351 of the Public Health Service Act (41 U.S.C. 262):* November 1, 2000. FDA has verified the applicant's claim that the biologics license application (BLA) for ZEVALIN (BLA 1250190) was initially submitted on November 1, 2000.

3. *The date the application was approved:* February 19, 2002. FDA has verified the applicant's claim that BLA 1250190 was approved on February 19, 2002.

This determination of the regulatory review period establishes the maximum potential length of a patent extension. However, the U.S. Patent and Trademark Office applies several statutory limitations in its calculations of the actual period for patent extension. In its application for patent extension, this applicant seeks 227 days of patent term extension.

Anyone with knowledge that any of the dates as published are incorrect may submit to the Dockets Management Branch (*see ADDRESSES*) written or electronic comments and ask for a redetermination by June 20, 2003. Furthermore, any interested person may petition FDA for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period by October 20, 2003. To meet its burden, the petition must contain sufficient facts to merit an FDA investigation. (*See H. Rept. 857, part 1, 98th Cong., 2d sess., pp. 41-42, 1984.*) Petitions should be in the format specified in 21 CFR 10.30.

Comments and petitions should be submitted to the Dockets Management Branch (*see ADDRESSES*). Three copies of any mailed information are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments and petitions may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

Dated: March 31, 2003.

Jane A. Axelrad,

Associate Director for Policy, Center for Drug Evaluation and Research.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 01E-0031]

Determination of Regulatory Review Period for Purposes of Patent Extension; EXELON

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined the regulatory review period for EXELON and is publishing this notice of that determination as required by law. FDA has made the determination because of the submission of an application to the Director of Patents and Trademarks, Department of Commerce, for the extension of a patent which claims that human drug product.

ADDRESSES: Submit written comments and petitions to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>.

FOR FURTHER INFORMATION CONTACT: Claudia Grillo, Office of Regulatory Policy (HFD-013), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-3460.

SUPPLEMENTARY INFORMATION: The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) and the Generic Animal Drug and Patent Term Restoration Act (Public Law 100-670) generally provide that a patent may be extended for a period of up to 5 years so long as the patented item (human drug product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For human drug products, the testing phase begins when the exemption to permit the clinical investigations of the drug becomes effective and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the human drug product and continues until FDA grants permission to market the drug product. 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 a human drug product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(1)(B).

FDA recently approved for marketing the human drug product EXELON (rivastigmine tartrate). EXELON is indicated for the treatment of mild to moderate dementia of the Alzheimer's type. Subsequent to this approval, the Patent and Trademark Office received a patent term restoration application for EXELON (U.S. Patent No. 4,948,807) from Novartis, and the Patent and Trademark Office requested FDA's assistance in determining this patent's eligibility for patent term restoration. In a letter dated May 2, 2001, FDA advised the Patent and Trademark Office that this human drug product had undergone a regulatory review period and that the approval of EXELON represented the first permitted commercial marketing or use of the product. Shortly thereafter, the Patent and Trademark Office requested that FDA determine the product's regulatory review period.

FDA has determined that the applicable regulatory review period for EXELON is 3,424 days. Of this time, 2,313 days occurred during the testing phase of the regulatory review period, while 1,111 days occurred during the approval phase. These periods of time were derived from the following dates:

1. *The date an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(i)) became effective:* December 8, 1990. The applicant claims November 7, 1990, as the date the investigational new drug application (IND) became effective. However, FDA records indicate that the IND effective date was December 8, 1990, which was 30 days after FDA receipt of the IND.

2. *The date the application was initially submitted with respect to the human drug product under section 505(b) of the act:* April 7, 1997. FDA has verified the applicant's claim that the new drug application (NDA) for EXELON (NDA 20-823) was initially submitted on April 7, 1997.

3. *The date the application was approved:* April 21, 2000. FDA has verified the applicant's claim that NDA 20-823 was approved on April 21, 2000.

This determination of the regulatory review period establishes the maximum potential length of a patent extension. However, the U.S. Patent and

Trademark Office applies several statutory limitations in its calculations of the actual period for patent extension. In its application for patent extension, this applicant seeks 1,825 days of patent term extension.

Anyone with knowledge that any of the dates as published are incorrect may submit to the Dockets Management Branch (*see ADDRESSES*) written or electronic comments and ask for a redetermination by June 20, 2003. Furthermore, any interested person may petition FDA for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period by October 20, 2003. To meet its burden, the petition must contain sufficient facts to merit an FDA investigation. (*See H. Rept. 857, part 1, 98th Cong., 2d sess., pp. 41-42, 1984.*) Petitions should be in the format specified in 21 CFR 10.30.

Comments and petitions should be submitted to the Dockets Management Branch (*see ADDRESSES*). Three copies of any information are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments and petitions may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

Dated: March 31, 2003.

Jane A. Axelrad,

Associate Director for Policy, Center for Drug Evaluation and Research.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 03D-0120]

Medical Devices: Draft Guidance for Industry and FDA Reviewers; Multiplex Tests for Heritable DNA Markers, Mutations, and Expression Patterns; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of the draft guidance for industry entitled "Multiplex Tests for Heritable DNA Markers, Mutations, and Expression Patterns." FDA has received many inquiries pertaining to multiplex test submissions (including microarray submissions). This draft guidance document represents the Center for

Devices and Radiological Health's (CDRH) attempt to continue the dialogue with stakeholders regarding the basic framework for the types of data that should be included in a submission. FDA is anxious to provide the best guidance possible to assist sponsors in developing multiplex text submissions that will support timely review and marketing of safe and effective products using this technology. This draft guidance document is neither final nor is it in effect at this time.

DATES: Submit written or electronic comments on this draft guidance document by July 21, 2003.

ADDRESSES: Submit written requests for single copies on a 3.5" diskette of the draft guidance entitled "Multiplex Tests for Heritable DNA Markers, Mutations, and Expression Patterns" to the Division of Small Manufacturers, International, and Consumer Assistance (HFZ-220), Center for Devices and Radiological Health, Food and Drug Administration, 1350 Piccard Dr., Rockville, MD 20850. Send two self-addressed adhesive labels to assist that office in processing your request or fax your request to 301-443-8818. *See the SUPPLEMENTARY INFORMATION* section for information on electronic access to the draft guidance document.

Submit written comments on this draft guidance to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>. Identify comments with the docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT:

Elizabeth Mansfield or Michele Schoonmaker, Center for Devices and Radiological Health (HFZ-440), Food and Drug Administration, 2098 Gaither Rd., Rockville, MD 20850, 301-594-1293.

SUPPLEMENTARY INFORMATION:

I. Background

FDA anticipates that multiplex tests, including such as microarrays, using DNA and ribonuclei acid samples will be anticipated to have a number of clinical purposes, including genotyping, haplotype analysis, and categorization by expression profile, etc. FDA has received many inquiries pertaining to possible regulatory strategies for submitting and reviewing data from assays yielding multiple, simultaneous results. Over the past 24 months, FDA has participated in a number of seminars and workshops with representatives from the drug and